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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: TANIGUCHI Kiyoshi et al.
SERIAL NO.: NEW U.S. PCT APPLICATION
FILED: HEREWITH
INTERNATIONAL APPLICATION NO.: PCT/JP00/00018
INTERNATIONAL FILING DATE: January 6, 2000
FOR: CYCLIC COMPOUND

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119 AND THE INTERNATIONAL CONVENTION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

COUNTRY	APPLICATION NO	DAY/MONTH/YEAR
Australia	PP 8068	07 January 1999
Australia	PQ 1702	19 July 1999

Certified copies of the corresponding Convention application(s) were submitted to the International Bureau in PCT Application No. PCT/JP00/00018. Receipt of the certified copy(s) by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

Respectfully submitted,
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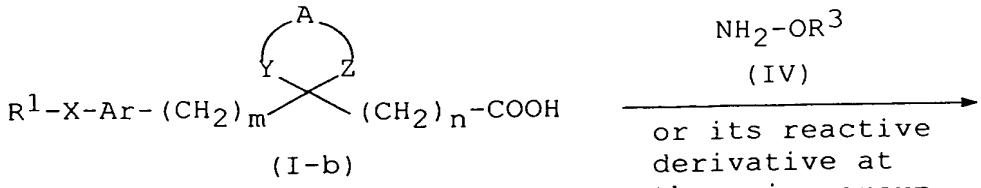
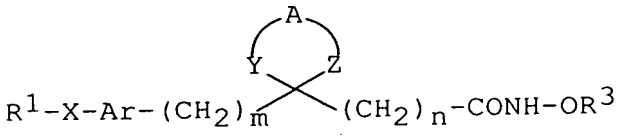
Process 4



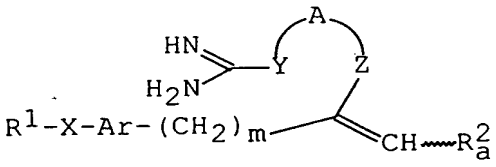
(I-b)
or its reactive derivative at the carboxy-group, or a salt thereof

NH_2-OR^3
(IV)
or its reactive derivative at the amino-group, or a salt thereof



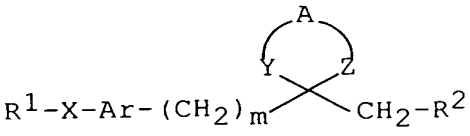
(I-e)
or a salt thereof

Process 5



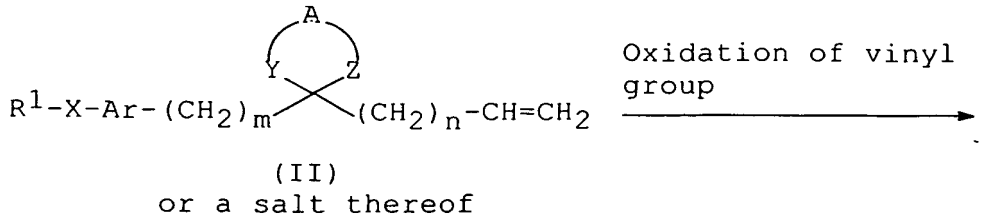
(III)
or a salt thereof

Cyclization

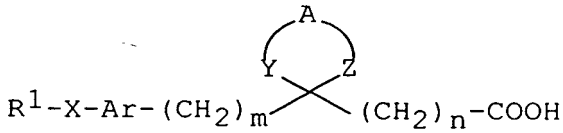


(I-f)
or a salt thereof

Process 2

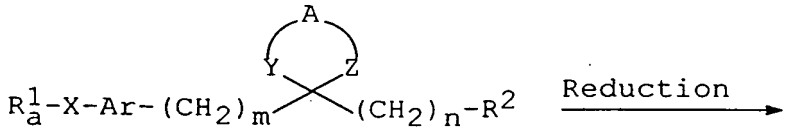


(II)
or a salt thereof

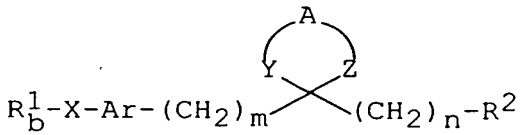


(I-b)
or a salt thereof

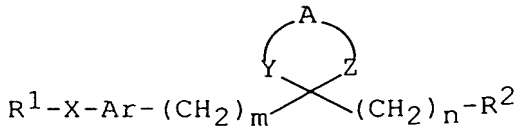
Process 3



(I-c)
or a salt thereof



(I-d)
or a salt thereof



(I)

in which R^1 is lower alkyl, halogen, optionally substituted heterocyclic group or optionally substituted aryl,

R^2 is carboxy, protected carboxy or amidated carboxy,

Ar is optionally substituted aryl or optionally substituted heterocyclic group,

A is lower alkylene,

X is oxa or a single bond,

Y is thia, sulfinyl or sulfonyl,

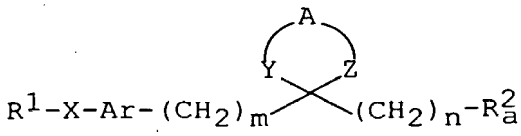
Z is methylene, thia, sulfinyl or sulfonyl,

m and n are each an integer of 0 to 6, and $1 \leqq m+n \leqq 6$,

and its salt.

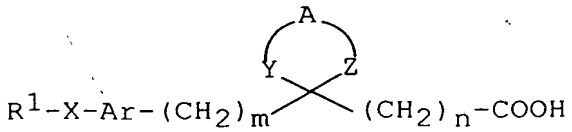
The object compounds of the present invention can be prepared by the following processes.

Process 1



(I-a)
or a salt thereof

Removal of the carboxy-protective group



(I-b)
or a salt thereof

provide a method for using the same for the treatment and/or the prevention of MMP- or TNF α-mediated diseases in mammals, especially humans.

The compounds of the present invention have inhibitory activity on MMP or the production of TNF α, and are useful for the treatment and/or prevention of diseases such as stroke, arthritis, cancer, tissue ulceration, decubitus ulcer, restenosis, periodontal disease, epidermolysis bullosa, scleritis, psoriasis and other diseases characterized by matrix metalloproteinase activity, as well as AIDS, sepsis, septic shock and other diseases caused by the production of TNF α.

There are a number of structurally related metalloproteases which effect the breakdown of structural proteins. Matrix-degrading metalloproteases, such as gelatinase (MMP-2, MMP-9), stromelysin (MMP-3) and collagenase (MMP-1, MMP-8, MMP-13), are involved in tissue matrix degradation and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g., osteoarthritis and rheumatoid arthritis, etc.), cerebral disease (e.g., stroke, etc.), tissue ulceration (e.g., corneal, epidermal and gastric ulcerations, etc.), abnormal wound healing, periodontal disease, bone disease (e.g., Paget's disease and osteoporosis, etc.), tumor metastasis or invasion and HIV-infection.

A tumor necrosis factor is recognized to be involved in many infections and autoimmune diseases. Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock.

The object compounds of the present invention are novel and can be represented by the following formula (I) :

Fujisawa Pharmaceutical Co., Ltd.

A U S T R A L I A
Patents Act 1990

PROVISIONAL SPECIFICATION
for the invention entitled:

"Cyclic Compound"

The invention is described in the following statement:

DESCRIPTION

CYCLIC COMPOUND

Field of the Invention

The present invention relates to new compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to new compounds and pharmaceutically acceptable salts thereof which are useful as inhibitors of matrix metalloproteinases (hereinafter to be referred to as MMP) or the production of tumor necrosis factor α (hereinafter to be referred to as TNF α), to pharmaceutical compositions comprising the same, to use of the same as medicaments, and to methods for using the same therapeutically in the treatment and/or the prevention of MMP- or TNF α-mediated diseases.

Background Art

Some compounds to be useful as metalloproteinase inhibitors, or the like are known (WO 97/20824, etc.).

Disclosure of the Invention

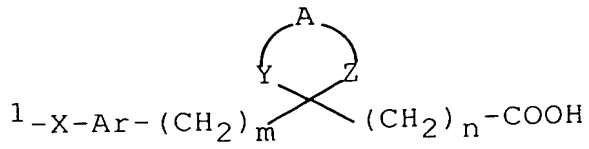
One object of the present invention is to provide new and useful cyclic compounds and pharmaceutically acceptable salts thereof, and to provide a process for preparing said new cyclic compound and salts thereof, which have pharmacological activities such as MMP- or TNF α- inhibitory activity and the like.

Another object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said cyclic compound or a pharmaceutically acceptable salt thereof.

A further object of the present invention is to provide use of said cyclic compounds and pharmaceutically acceptable salts thereof as medicaments for prophylactic and therapeutic treatment of MMP- or TNF α-mediated diseases.

A still further object of the present invention is to

Process 6

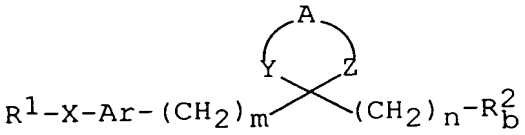


(I-b)

or its reactive derivative at the carboxy-group, or a salt thereof

Optically active amine

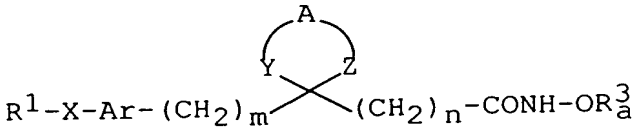
or its reactive derivative at the amino-group, or a salt thereof



(I-g)

or a salt thereof

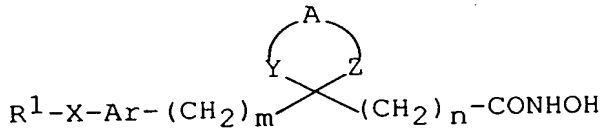
Process 7



(I-h)

or a salt thereof

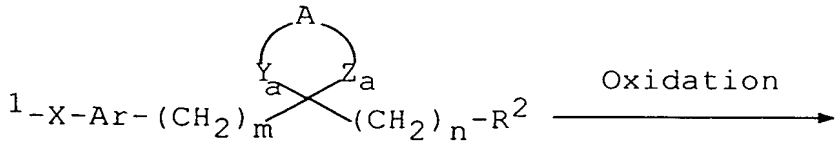
Removal of the hydroxy-protective group



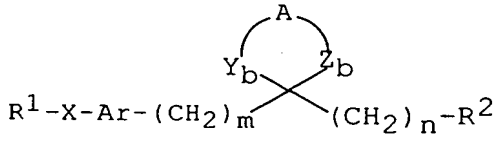
(I-i)

or a salt thereof

Process 8

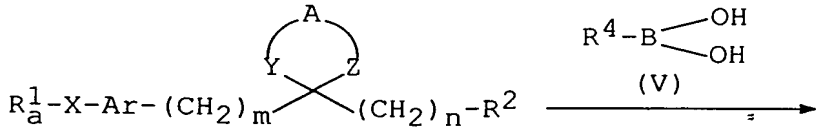


(I-j)
or a salt thereof

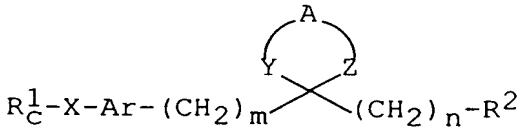


(I-k)
or a salt thereof

Process 9

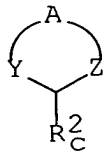


(I-c)
or a salt thereof



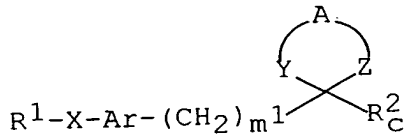
(I-l)
or a salt thereof

Process 10



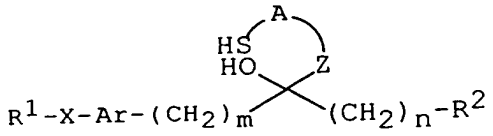
(VI)
or a salt thereof

R^1-X-Ar-$(CH_2)_{m1}$-L
(VII)
or a salt thereof



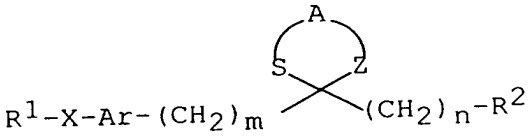
(I-m)
or a salt thereof

Process 11



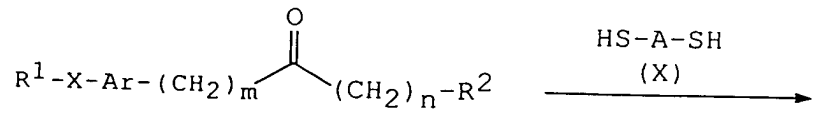
(VIII)
or a salt thereof

Cyclization

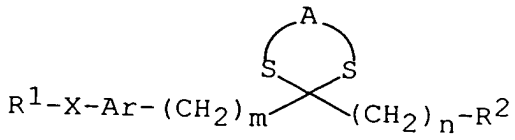


(I-n)
or a salt thereof

Process 12



(IX)
or a salt thereof



(I-o)
or a salt thereof

in which R^1, R^2, Ar, A, X, Y, Z, m and n are each as defined above,

R^1_a is haloaryl,

R^1_b is aryl,

R^1_c is aryl substituted by optionally substituted aryl,

R^2_a is protected carboxy,

R^2_b is optically active amide,

R^2_c is protected carboxy,

R^3 is hydrogen or hydroxy-protective group,

R^3_a is hydroxy-protective group,

R^4 is optionally substituted aryl,

Y_a is thia, sulfinyl or sulfonyl,

Z_a is methylene, thia, sulfinyl or sulfonyl, provided that at least one of Y_a and Z_a is thia or sulfinyl,

Y_b is thia, sulfinyl or sulfonyl,

Z_b is methylene, thia, sulfinyl or sulfonyl,

provided that at least one of
Y_b and Z_b is sulfinyl or sulfonyl,
L is a leaving group, and
m^1 is an integer of 1 to 6.

The starting compounds used in the above processes can be prepared according to the following Preparations or by a conventional method.

Suitable salts of the object compound (I) may be conventional non-toxic pharmaceutically acceptable salts and include an acid addition salt such as an organic acid salt (e.g., acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.), or a salt with a base such as an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzyl-ethylenediamine salt, etc.), or the like.

The object compounds and pharmaceutically acceptable salts thereof may include solvates such as enclosure compounds (e.g., hydrate, etc.).

Suitable examples and illustrations of the various definitions, which the present invention includes within its scope and which are shown in the above and subsequent descriptions of the present specification, are as follows.

Suitable "aryl" and aryl moiety in the term "optionally substituted aryl" may include an aryl having 6 to 10 carbon atoms, such as phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl and the like, preferably phenyl.

Suitable "optionally substituted aryl" may include above-mentioned aryl, which is substituted by a suitable substituent(s) such as halogen, lower alkyl, lower alkoxy, halo(lower)alkyl, halo(lower)alkoxy, lower alkenyl, or acyl, lower alkylthio, aryl, haloaryl, hydroxy, hydroxy(lower)alkyl, amino, carboxy, protected carboxy, nitro(lower)alkenyl, lower alkylenedioxy, acylamino, nitro, and the like.

Preferable examples of optionally substituted aryl may be phenyl, halophenyl (e.g. chlorophenyl, bromophenyl, fluorophenyl, etc.), halophenylphenyl (e.g. fluorophenylphenyl, etc.) for R^1 and phenyl for Ar, and the most preferable one may be phenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl and 4-(4-fluorophenyl)phenyl for R^1, and phenyl for Ar.

Suitable "heterocyclic group" in the term "optionally substituted heterocyclic group" means saturated or unsaturated, 3- to 8-membered monocyclic or polycyclic heterocyclic group containing at least one hetero atom such as oxygen atom, sulfur atom, nitrogen atom and the like.

Preferable heterocyclic groups are :

-unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), and the like;

-saturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperidino, pyrazolidinyl, piperazinyl, and the like;

9- or 10-membered, heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, qinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), dihydrotriazolopyridazinyl, and the like;

-unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), and the like;

-saturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, morpholinyl, morpholino, and the like;

-unsaturated condensed 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, benzoxazolyl, benzoxadiazolyl, and the like;

-unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl, etc.), and the like;

-saturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolidinyl, and the like;

-unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 sulfur atoms, for example, thienyl, and the like;

-unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms, for example, furyl, and the like;

-saturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms, for example, oxolanyl, and the like;

-unsaturated condensed 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, benzothiazolyl, benzothiadiazolyl, and the like;

-unsaturated condensed 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 or 2 oxygen atoms, for example, benzofuranyl, benzodihydrofuranyl, benzodioxolenyl, and the like;

-unsaturated condensed 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 or 2 sulfur atoms, for example, benzothiophenyl, dihydrobenzothiophenyl, and the like; etc.

More preferable heterocyclic groups may be unsaturated 5- or 6-membered heteromonocyclic group containing 1 or 2 sulfur atoms, and the most preferable one may be thienyl.

These heterocyclic groups may have one or more substituents. Examples of the substituents for substituted heterocyclic group may be the same as those for "optionally substituted aryl".

The term "lower" is intended to mean up to 6 carbon atoms, preferably up to 4 carbon atoms, unless otherwise indicated.

Suitable "lower alkyl" may include a straight or branched alkyl having 1 to 6 carbon atoms, and exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl and the like, and the most preferably methyl for R^1.

Suitable "lower alkenyl" may include a straight or branched alkenyl having 2 to 6 carbon atoms, and exemplified by ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl and the like.

Suitable "lower alkoxy" may include a straight or

branched alkenyl having 1 to 6 carbon atoms, and exemplified by methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, hexyloxy and the like.

Suitable "hydroxy-protective group" may include a conventional protective group, for example, substituted lower alkyl such as lower alkoxy(lower)alkyl (e.g., methoxymethyl), lower alkoxy(lower)alkoxy(lower)alkyl (e.g., methoxyethoxymethyl) and substituted or unsubstituted aryl(lower)alkyl (e.g., benzyl nitrobenzyl); acyl such as lower alkanoyl (e.g., acetyl, propionyl, pivaloyl), aroyl (e.g., benzoyl, fluorenecarbonyl), lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl), substituted or unsubstituted aryl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl, bromobenzyloxycarbonyl), arenesulfonyl (e.g., benzenesulfonyl, tosyl) and alkanesulfonyl (e.g., methanesulfonyl, ethanesulfonyl); tri(lower)alkylsilyl (e.g., trimethylsilyl); tetrahydropyranyl; and the like, preferably tetrahydropyranyl.

Suitable "halogen" includes fluorine, bromine, chlorine and iodine.

Suitable acyl moiety of "acylamino" includes acyl such as aliphatic acyl, aromatic acyl, heterocyclic acyl and aliphatic acyl substituted by aromatic or heterocyclic group(s) derived from carboxylic, carbonic, sulfonic and carbamic acids.

The aliphatic acyl includes saturated or unsaturated, acyclic or cyclic ones, for example, alkanoyl such as lower alkanoyl (e.g., formyl, acetyl, propionyl, butylyl, isobutylyl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), alkylsulfonyl such as lower alkylsulfonyl (e.g., mesyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, pentylsulfonyl,

hexylsulfonyl, etc.), carbamoyl, N-alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), alkoxycarbonyl such as lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, etc.), alkenyloxycarbonyl such as lower alkenyloxycarbonyl (e.g., vinyloxycarbonyl, allyloxycarbonyl, etc.), alkenoyl such as lower alkenoyl (e.g., acryloyl, methacryloyl, crotonoyl, etc.), cycloalkanecarbonyl such as cyclo(lower)alkanecarbonyl (e.g., cyclopropanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, etc.), and the like.

The aromatic acyl may include C_6-C_{10} aroyl (e.g., benzoyl, toluoyl, xyloyl, etc.), N-(C_6-C_{10})arylcarbamoyl (e.g., N-phenylcarbamoyl, N-tolylcarbamoyl, N-naphthylcarbamoyl, etc.), C_6-C_{10} arenesulfonyl (e.g., benzenesulfonyl, tosyl, etc.), and the like.

The heterocyclic acyl may include heterocyclic-carbonyl (e.g., furoyl, thenoyl, nicotinoyl, isonicotinoyl, thiazolylcarbonyl, thiadiazolylcarbonyl, tetrazolylcarbonyl, etc.), and the like.

The aliphatic acyl substituted by aromatic group(s) may include aralkanoyl such as phenyl(lower)alkanoyl (e.g., phenylacetyl, phenylpropionyl, phenylhexanoyl, etc.), aralkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, etc.), aryloxyalkanoyl such as phenoxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.), and the like.

The aliphatic acyl substituted by heterocyclic group(s) may include heterocyclic-alkanoyl such as heterocyclic-(lower)alkanoyl (e.g., thienylacetyl, imidazolylacetyl, furylacetyl, tetrazolylacetyl, thiazolylacetyl, thiadiazolylacetyl, thienylpropionyl, thiadiazolylpropionyl, etc.), and the like.

These acyl groups may be further substituted by one or more suitable substituents such as nitro and the like, and

preferable acyl having such substituent(s) may be nitroaralkoxycarbonyl (e.g., nitrobenzyloxycarbonyl, etc.) and the like.

Suitable "protected carboxy" includes esterified carboxy wherein "esterified carboxy" is as defined below.

Suitable examples of the ester moiety of the esterified carboxy are lower alkyl ester (e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, etc.) and the like, which may have at least one suitable substituent. Examples of the substituted lower alkyl ester are lower alkanoyloxy(lower)alkyl ester [e.g., acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1-(or 2-)acetoxyethyl ester, 1-(or 2- or 3-)acetoxypropyl ester, 1-(or 2- or 3- or 4-)-acetoxybutyl ester, 1-(or 2-)propionyloxyethyl ester, 1-(or 2- or 3-)propionyloxypropyl ester, 1-(or 2-)-butyryloxyethyl ester, 1-(or 2-)isobutyryloxyethyl ester, 1-(or 2-)pivaloyloxyethyl ester, 1-(or 2-)hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1-(or 2-)-pentanoyloxyethyl ester, etc.], lower alkanesulfonyl(lower)-alkyl ester (e.g., 2-mesylethyl ester, etc.), mono(or di or tri)halo(lower)alkyl ester (e.g., 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.);
lower alkoxycarbonyloxy(lower)alkyl ester [e.g., methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester, tert-butoxycarbonyloxymethyl ester, 1-(or 2-)methoxycarbonyloxyethyl ester, 1-(or 2-)ethoxycarbonyloxyethyl ester, 1-(or 2-)isopropoxycarbonyloxyethyl ester, etc.],
phthalidylidene(lower)alkyl ester, (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g., (5-methyl-2-oxo-1,3-

dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.]; lower alkenyl ester (e.g., vinyl ester, allyl ester, etc.); lower alkynyl ester (e.g., ethynyl ester, propynyl ester, etc.); ar(lower)alkyl ester which may have at least one suitable substituent (e.g., benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.); aryl ester which may have at least one suitable substituent (e.g., phenyl ester, 4-chlorophenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.); phthalidyl ester; and the like.

More preferable example of the protected carboxy thus defined may be C_1-C_4 alkoxycarbonyl, and the most preferable one may be methoxycarbonyl and ethoxycarbonyl.

Said "amidated carboxy" can be referred to the ones as mentioned below.

Suitable examples of the amidated carboxy may include optionally substituted carbamoyl such as

-carbamoyl,

-N-hydroxycarbamoyl,

-N-(protected hydroxy)carbamoyl, wherein said hydroxy-protective group may be the same as mentioned above (e.g. tetrahydropyranyl, etc.),

-mono(or di)(lower)alkylcarbamoyl wherein the lower alkyl group may be the same as those mentioned above (e.g. methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, 3-methylbutylcarbamoyl, isobutylcarbamoyl, pentylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, etc.),

-N-(aryl(lower)alkyl)carbamoyl such as phenyl(lower)-alkylcarbamoyl (e.g. 1-phenylethylcarbamoyl, (R)-(+)-1-phenylethyl, etc.),

-(C_3-C_7)cycloalkylcarbamoyl (e.g. cyclohexylcarbamoyl, etc.),

-(C_3-C_7)cycloalkylcarbamoyl (e.g. cyclohexylcarbamoyl, etc.),
-carbamoyl substituted by amino or di(lower)alkylamino [e.g. N-aminocarbamoyl, N-(dimethylamino)carbamoyl, etc.],
-lower alkyleneaminocarbonyl (e.g. pyrrolidin-1-ylcarbonyl, hexahydro-1H-azepin-1-ylcarbonyl, etc.),
said alkylene being optionally substituted by carboxy or protected carboxy as mentioned above such as lower alkoxycarbonyl [e.g. carboxypyrrolidin-1-ylcarbonyl, (methoxycarbonyl)pyrrolidin-1-ylcarbonyl, (ethoxycarbonyl)pyrrolidin-1-ylcarbonyl, etc.],
or said lower alkylene being optionally interrupted by other hetero atom(s) such as nitrogen, oxygen or sulfur (e.g. morpholinocarbonyl, etc.),
-lower alkylsulfonylcarbamoyl (e.g. methylsulfonylcarbamoyl, etc.),
-arenesulfonylcarbamoyl (e.g. benzenesulfonylcarbamoyl, etc.), and the like.

Preferable example of the amidated carboxy thus defined may be :
-N-hydroxycarbamoyl,
-N-tetrahydropyranyloxycarbamoyl, and
-N-(phenylethyl)carbamoyl.

Suitable "leaving group" may include halogen as mentioned above, acyloxy such as sulfonyloxy (e.g., mesyloxy, tosyloxy, etc.), alkoxy (e.g., tert-butoxy, etc.), aralkoxy (e.g., benzyloxy, etc.), and the like, preferably halogen and the most preferably bromine.

Suitable "lower alkylene" may include straight or branched one such as methylene, ethylene, trimethylene,

hexamethylene, and the like, in which more preferable one may be C_1-C_4 alkylene, and the most preferable one may be ethylene 1-methyltrimethylene, and trimethylene.

Suitable "halo(lower)alkyl" may be above-mentioned lower alkyl substituted by halogen as mentioned above, in which more preferable one may be halo(C_1-C_4)alkyl.

Suitable "halo(lower)alkoxy" may be above-mentioned lower alkoxy substituted by halogen as mentioned above, in which more preferable one may be halo(C_1-C_4)alkoxy.

Suitable "lower alkylthio" may be thio group substituted by above-mentioned lower alkyl, in which more preferable one may be C_1-C_4 alkylthio.

Suitable "haloaryl may be aforementioned aryl substituted by halogen as mentioned above, in which more preferable one may be halo(C_6-C_{10})aryl, and the most preferable one may be 4-fluorophenyl.

Suitable "hydroxy(lower)alkyl" may be above-mentioned lower alkyl substituted by hydroxy as mentioned above, in which more preferable one may be hydroxy(C_1-C_4)alkyl.

Suitable "nitro(lower)alkenyl" may be above-mentioned lower alkenyl substituted by nitro, in which more preferable one may be nitro(C_2-C_4)alkenyl.

Suitable "lower alkylenedioxy" may include straight or branched one such as methylenedioxy, ethylenedioxy, trimethylenedioxy, propylenedioxy, tetramethylenedioxy, ethylethylenedioxy, pentamethylenedioxy, hexamethylenedioxy, and the like, in which more preferable one may be C_1-C_4 alkylenedioxy.

Suitable "acylamino" may be amino substituted by acyl as mentioned above, in which more preferable one may be lower alkanoylamino.

In the object compounds (I),

(i) the preferred one may be the compounds (I) wherein m and n are each 0 or 1, and

(ii) the more preferred one may be the compounds of the above item (i) wherein A is ethylene, 1-methyltrimethylene, or trimethylene.

The processes for preparing the object compounds are explained in detail in the following.

Process 1

The object compound (I-b) or a salt thereof can be prepared by subjecting a compound (I-a) or a salt thereof to removal reaction of the carboxy-protective group.

Suitable salts of the compounds (I-a) and (I-b) can be referred to the ones as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional method such as solvolysis including hydrolysis, reduction or the like.

The solvolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, lithium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, hydrazine, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]-non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include and organic acid [e.g. formic

acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, hydrogen fluoride, boron trifluoride diethyl etherate, hydrogen iodide, etc.].

The removal reaction using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like, is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, chloroform, carbon tetrachloride, dioxane, tetrahydrofuran, N,N-dimethylformamide, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reduction method applicable for the removal reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction may include a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel,

catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like, and these catalysts may be used in a combination with ammonium formate (e.g. a combination of palladium on carbon and ammonium formate, etc.).

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acid to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

Process 2

The compound (I-b) or a salt thereof can be prepared by oxidating the compound (II) or a salt thereof.

Suitable salts of the compound (II) may be the same as those for the compound (I).

Oxidation is carried out in a conventional manner, which is capable of oxidating a vinyl group to a carboxy group, and suitable oxidizing reagent may be oxygen acid such as periodate (e.g. sodium periodate, potassium periodate, etc.), peroxy acid such as perbenzoic acid (e.g., perbenzoic acid, m-chloroperbenzoic acid, etc.), OXONE ($2KHSO_5 \cdot KHSO4 \cdot K_2SO_4$), potassium permanganate, a combination of titanium (III) chloride and hydrogen peroxide, a combination thereof (e.g. a combination of potassium permanganate and sodium periodate,

This reaction can be carried out in the presence of a suitable base as mentioned above (e.g. potassium carbonate, etc.).

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, t-butyl alcohol, etc.), tetrahydrofuran, dioxane, dichloromethane, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other organic solvent which does not adversely affect the reaction.

Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 3

The compound (I-d) or a salt thereof can be prepared by subjecting the compound (I-c) or a salt thereof to a reduction reaction.

Suitable salts of the compounds (I-c) and (I-d) may be the same as those for the compound (I).

The reduction method applicable for this reaction may be the same as Process 1, which is capable of converting haloaryl group to aryl group (e.g. a combination of palladium on carbon and ammonium formate, etc.).

Process 4

The compound (I-e) or a salt thereof can be prepared by reacting the compound (I-b) or its reactive derivative at the carboxy group, or a salt thereof with compound (IV) or its reactive derivative at the amino group, or a salt thereof.

Suitable reactive derivative at the amino group of the compound (IV) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (IV) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction

of the compound (IV) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (IV) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (IV) and its reactive derivative can be referred to the acid addition salts as exemplified for the compound (I).

Suitable salts of the compound (I-e) may be the same as those for the compound (I).

Suitable reactive derivative at the carboxy group of the compound (I-b) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride which acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl

thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (I-b) to be used.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (I-b) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSCD); N,N'-carbonylbis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)-isoxazolium hydroxide intramolecular salt; N-hydroxybenzotriazole; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared

by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base as mentioned above such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, alkali metal hydroxide, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 5

The object compound (I-f) or a salt thereof can be prepared by cyclizing the compound (III) or a salt thereof.

Suitable salts of the compounds (I-f) and (III) may be the same as those for the compound (I).

This reaction is preferably carried out in the presence of hydrogen halide (e.g. hydrogen iodide, etc.) or alkali metal halide (e.g. sodium iodide, etc.).

This reaction can be carried out in the presence of a suitable base as mentioned above such as alkali metal hydroxide.

The reaction can be carried out in a conventional solvent, which does not adversely influence the reaction as mentioned above such as water, tetrahydrofuran, alcohol (e.g. methanol, ethanol, etc.), a mixture thereof, and the like.

The reaction temperature is not critical and the reaction can be carried out under from warming to heating.

Process 6

The compound (I-g) or a salt thereof can be prepared by reacting the compound (I-b) or its reactive derivative at the carboxy group, or a salt thereof, with an optically active amine or its reactive derivative at the amino group, or a salt thereof.

Suitable "optically active amine" may include a conventional one which is capable of separating the starting racemic compound into each optically active compound such as (R)-(+)-α-methylbenzylamine, and the like.

Suitable salts of the compound (I-g) may be the same as those exemplified for the compound (I).

Suitable salts of the optically active amine may be acid addition salts as mentioned for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine and dichloromethane, a mixture thereof, or any other organic solvents which do not adversely affect the reaction.

This reaction can be carried out in the presence of an organic or inorganic base such as alkali metal (e.g. lithium, sodium, potassium, etc.), alkaline earth metal (e.g., calcium, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkaline earth metal hydride (e.g., calcium hydride, etc.), alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate (e.g., sodium bicarbonate, potassium bicarbonate, etc.), alkali metal alkoxide (e.g., sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoic acid (e.g., sodium acetate, etc.), trialkylamine (e.g., triethylamine, etc.), pyridine compound (e.g., pyridine, lutidine, picoline, 4-dimethylaminopyridine, etc.), quinoline, lithium diisopropylamide, and the like.

Suitable reactive derivative at the amino group of optically active amine may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the said amine with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the said amine with a silyl compound such as

bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by the reaction of the said amine with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative at the carboxy group and salts of the compound (I-b) may be the same as mentioned above.

The reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate (e.g., ethyl chloroformate, isopropyl chloroformate); triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; 1-hydroxybenzotriazole; or so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride or oxalyl chloride.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 7

The compound (I-i) or a salt thereof can be prepared by

subjecting the compound (I-h) or a salt thereof to a removal reaction of the hydroxy protective group.

Suitable salts of the compound (I-h) and (I-i) may be the same as those exemplified for the compound (I).

The reaction of this process can be carried out in a manner similar to that in Process 1.

Process 8

The compound (I-k) and a salt thereof can be prepared by oxidating the compound (I-j) or a salt thereof.

Suitable salts of the compounds (I-j) and (I-k) may be the same as those exemplified above with regard to the compound (I).

Suitable method of this oxidation includes conventional ones, which can convert thia group to sulfinyl or sulfonyl group, or sulfinyl to sulfonyl group, such as exemplified for Process 2.

Process 9

The compound (I-l) or a salt thereof can be prepared by reacting the compound (I-c) or a salt thereof with the compound (V).

Suitable salts of the compound (I-l) may be the same as those exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine and dichloromethane, a mixture thereof, or any other organic solvents which do not adversely affect the reaction.

This reaction can be carried out in the presence of an organic or inorganic base such as alkali metal (e.g., lithium, sodium, potassium, etc.), alkaline earth metal (e.g., calcium, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkaline earth metal hydride (e.g., calcium

hydride, etc.), alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate (e.g., sodium bicarbonate, potassium bicarbonate, etc.), alkali metal alkoxide (e.g., sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoic acid (e.g., sodium acetate, etc.), trialkylamine (e.g., triethylamine, etc.), pyridine compound (e.g., pyridine, lutidine, picoline, 4-dimethylaminopyridine, etc.), quinoline, lithium diisopropylamide, alkali metal halide (e.g., sodium iodide, potassium iodide, etc.), alkali metal thiocyanate (e.g., sodium thiocyanate, potassium thiocyanate, etc.), di(lower)alkyl azodicarboxylate (e.g., diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.), and the like.

The reaction is preferably carried out in the presence of a conventional condensing agent such as
N,N'-dicyclohexylcarbodiimide;
N-cyclohexyl-N'-morpholinoethylcarbodiimide;
N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;
N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide;
N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide;
N,N'-carbonylbis-(2-methylimidazole);
pentamethyleneketene-N-cyclohexylimine;
diphenylketene-N-cyclohexylimine; ethoxyacetylene;
1-alkoxy-1-chloroethylene; trialkyl phosphite;
ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride);
phosphorus trichloride; diphenyl phosphorylazide;
thionyl chloride; oxalyl chloride; lower alkyl haloformate (e.g., ethyl chloroformate, isopropyl chloroformate);
triphenylphosphine; tetrakis(triphenylphosphine)palladium(0);
2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt;
1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole;

1-hydroxybenzotriazole; or so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride or oxalyl chloride.

The reaction temperature is not critical, and the reaction is usually carried out under from warming to heating.

Process 10

The compound (I-m) or a salt thereof can be prepared by reacting the compound (VI) or a salt thereof with the compound (VII) or a salt thereof.

Suitable salts of the compound (I-m) may be the same as those exemplified for the compound (I).

The reaction of this process can be carried out in a manner similar to that in Process 9.

Process 11

The compound (I-n) or a salt thereof can be prepared by cyclizing the compound (VIII) or a salt thereof.

Suitable salts of the compounds (I-n) and (VIII) may be the same as those exemplified for the compound (I).

This reaction can be carried out in the presence of a suitable acid as exemplified for Process 1, wherein preferable one may be trifluoroacetic acid, and the like.

The reaction can be carried out in a conventional solvent, which does not adversely influence the reaction as mentioned above such as water, tetrahydrofuran, alcohol (e.g. methanol, ethanol, etc.), a mixture thereof, and the like.

The reaction temperature is not critical and the reaction can be carried out under cooling to warming.

Process 12

The compound (I-o) or a salt thereof can be prepared by reacting the compound (IX) or a salt thereof with the

compound (X).

Suitable salts of the compounds (I-o) and (IX) may be the same as those exemplified for the compound (I).

This reaction can be carried out in the presence of a suitable acid as exemplified for Process 1, wherein preferable one may be boron trifluoride diethyl etherate, and the like.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine and dichloromethane, a mixture thereof, or any other organic solvents which do not adversely affect the reaction.

The reaction temperature is not critical and the reaction can be carried out under cooling to warming.

The compounds obtained above can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation and the like.

The object compounds can be transformed into their salts in a conventional manner.

It is to be noted that the object compounds may include one or more stereoisomers or optical isomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

Collagenases initiate the degradation of collagen in vertebrates and, in addition to their normal function in the metabolism of connective tissue and wound healing, they have been implicated to be involved in a number of pathological conditions such as joint destruction in rheumatoid arthritis, periodontal disease, corneal ulceration, tumor metastasis, osteoarthritis, decubitus restenosis after percutaneous transluminal coronary angiopsty, osteoporosis, psoriasis, chronic active hepatitis, autoimmune keratitis, and the like, and therefore the compounds of the present invention are

useful for treating and/or preventing such pathological conditions.

Inhibitory activity of MMP can be assayed by a conventional test method as mentioned below.

Test Methods :

Test Method 1 :

Inhibitory activity of human MMP-1

Human collagenase was prepared from the culture medium of human skin fibroblast stimulated with interleukin-1β (1 ng/ml). Latent collagenase was activated by incubation with tryspin (200 μg/ml) at 37°C for 60 minutes and the reaction was stopped by adding soybean trypsin inhibitor (800 μg/ml). Collagenase activity was determined using FITC-labeled calf skin type I collagen. FITC-collagen (2.5 mg/ml) was incubated at 37°C for 120 minutes with the activated collagenase and test compound in 50 mM Tris buffer (containing 5 mM $CaCl_2$, 200 mM NaCl and 0.02% NaN_3, pH 7.5). After stopping the enzyme reaction by adding the equal volume of 70% ethanol-200 mM Tris buffer (pH 9.5), the reaction mixture was centrifuged, and collagenase activity was estimated by measuring the fluorescence intensity of supernatant at 495 nm (excitation) and 520 nm (emission).

Test Method 2 :

Inhibitory activity of human MMP-9

The inhibitory activity of test compounds against human MMP-9 were measured by using commercial kits (Yagai, Japan). Gelatinolytic activity was determined by monitoring the degradation of FITC-labeled bovine type IV collagen after incubation for 4 hours at 42°C. The amount of degraded collagen was estimated by measuring the fluorescence intensity at 495 nm (excitation) and 520 nm (emission).

Test Method 3 :

Inhibitory activity of human MMP-13

The inhibitory potential of test compounds against human MMP-13 were assayed by using commercial kit (Chondrex, USA) contained truncated form of human recombinant MMP-13 and fluorogenic peptide substrate. Activity of human MMP-13 was determined by monitoring the degradation of fluorogenic peptide substrate after incubation for 1 hour at 35°C and estimated by measuring the fluorescence intensity of degraded peptide substrate at 495 nm (excitation) and 520 nm (emission).

For therapeutic purposes, the compounds and pharmaceutically acceptable salts thereof of the present invention can be used in the form of a pharmaceutical preparation containing, as an active ingredient, one of said compounds in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solutions, suspensions, emulsions, sublingual tablets, suppositories, ointments, and the like. If desired, there may be included, in these preparations, auxiliary substances, stabilizing agents, wetting agents, emulsifying agents, buffers and other commonly used additives.

While the dose of the compound will vary depending upon the age and condition of patient and the like, in the case of intravenous administration, a daily dose of 0.01 - 100 mg of the active ingredient per kg weight of a human being, and in the case of intramuscular administration, a daily dose of 0.05 - 100 mg of the same per kg weight of a human being, or in the case of oral administration, a daily dose of 0.1 - 100 mg of the same per kg weight of a human being, is generally given for the treatment of MMP or TNFα-mediated diseases.

In order to illustrate the usefulness of the object compound, the pharmacological test data of a representative compound of the compounds are shown in the following.

Inhibitory activity of MMP

1. Test Method
   Inhibitory activity of human MMP-13 as mentioned above.

2. Test Compound
   Compound of Example 15

3. Test Result

Test Compound	Inhibitory activity [IC_{50} (nM)]
Example 15	2.2

The following Preparations and Examples are given for the purpose of illustrating the present invention in detail.

to be continued on the next page

Preparation 1-1)

N-Chlorosuccinimide (2.67 g) was added gradually over 30 minutes to a stirred solution of tetrahydro-2H-thiopyran (2.04 g) in benzene (20 ml). The temperature was maintained at 20-30°C by intermittent external cooling. The mixture was stirred for 1 hour and rapidly filtered to remove succinimide. The filtrate was added to a solution of 4-anisylmagnesium bromide in diethyl ether which was prepared from 4-anisyl bromide (7.48 g) and magnesium turnings (0.875 g) in diethyl ether (36 ml) in a usual manner. The rate of addition was such that the temperature of the reaction was maintained between 10-15°C. The resultant mixture was stirred at room temperature for 17 hours and decomposed by the addition of ice and a 20% aqueous solution of sulfuric acid. The organic layer was separated, washed twice with water, once with 1N sodium hydroxide solution, twice with water, then once with brine, and dried over magnesium sulfate. Removal of the solvent, followed by washing with methanol, gave 3,4,5,6-tetrahydro-2-(4-methoxyphenyl)-2H-thiopyran (1.22 g) as a colorless powder.

mp : 82-85°C

IR (KBr) : 1610, 1514, 1252 cm^{-1}

NMR (DMSO-d_6, δ) : 1.35-1.65 (2H, m), 1.7-2.1 (4H, m), 2.56-2.64 (1H, m), 2.73-2.86 (1H, m), 3.72 (3H, s), 3.84 (1H, dd, J=11.0, 2.7Hz), 6.87 (2H, d, J=8.7Hz), 7.24 (2H, d, J=8.7Hz)

Anal. Calcd. for $C_{12}H_{16}OS$: C 69.19, H 7.74

Found : C 69.59, H 7.68

Preparation 1-2)

1.0M Solution of boron tribromide in dichloromethane (8.27 ml) was added dropwise to a stirred solution of 3,4,5,6-tetrahydro-2-(4-methoxyphenyl)-2H-thiopyran (718 mg) in dichloromethane (10 ml) under ice cooling and the resulting mixture was stirred for 3 hours while the

temperature was allowed to rise to room temperature. The reaction mixture was evaporated in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent : toluene - ethyl acetate) over silica gel (15.4 g) to afford 3,4,5,6-tetrahydro-2-(4-hydroxyphenyl)-2H-thiopyran (600 mg) as a colorless powder.

mp : 138-140.5°C

IR (KBr) : 3421 (br), 1241 cm^{-1}

NMR (DMSO-d_6, δ) : 1.35-1.65 (2H, m), 1.7-2.05 (4H, m), 2.58 (1H, br d, J=13.3Hz), 2.71-2.85 (1H, m), 3.78 (1H, dd, J=10.8, 2.5Hz), 6.68 (2H, d, J=8.5Hz), 7.11 (2H, d, J=8.5Hz), 9.32 (1H, s)

Preparation 1-3)

A mixture of 3,4,5,6-tetrahydro-2-(4-hydroxyphenyl)-2H-thiopyran (578 mg), 4-bromochlorobenzene (683 mg), 8-hydroxyquinoline (17.3 mg), potassium carbonate (247 mg), and copper (I) chloride (11.8 mg) in 1,3-dimethyl-2-imidazolidinone (1.73 g) was stirred at 150°C under a nitrogen atmosphere for 21 hours and cooled to room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with a 1N aqueous solution of sodium hydroxide and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent: n-hexane-toluene) over silica gel to afford 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran (417 mg) as a colorless powder.

mp : 69.5-70.5°C

IR (KBr) : 1274 cm^{-1}

NMR ($CDCl_3$, δ) : 1.45-1.77 (2H, m), 1.83-2.2 (4H, m), 2.66 (1H, m), 2.81-2.95 (1H, m), 3.84 (1H, dd, J=11.6, 2.6Hz), 6.88-6.97 (4H, m), 7.23-7.36 (4H, m)

Preparation 1-4)

An aqueous solution (23 ml) of OXONE ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, 1.82 g) was added dropwise to a suspension of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran (600 mg) in methanol (23 ml) under ice cooling and the resulting mixture was stirred at room temperature for 17 hours. The reaction mixture was mixed with an aqueous solution (10 ml) of sodium sulfite (746 mg) at room temperature, stirred at the same temperature for a while, and concentrated in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was washed with n-hexane to afford 2-[4-(4-chlorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran 1,1-dioxide (636 mg) as a colorless powder.

mp : 151.5-152°C

IR (KBr) : 1313, 1247, 1120 cm^{-1}

NMR ($CDCl_3$, δ) : 1.65 (1H, m), 2.04-2.26 (4H, m), 2.37-2.56 (1H, m), 2.96-3.13 (1H, m), 3.24 (1H, m), 4.01 (1H, dd, J=12.8, 3.1Hz), 6.92-7.03 (4H, m), 7.28-7.42 (4H, m)

(+) APCI MS m/z : 336 (M^++H)

Preparation 1-5)

1.5M Solution of lithium diisopropylamide mono tetrahydrofuran in cyclohexane (1.47 ml) was added dropwise to a stirred suspension of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran 1,1-dioxide (621 mg) in tetrahydrofuran (9 ml) under a nitrogen atmosphere and dry ice - acetone cooling and the resultant suspension was stirred under the same conditions for 25 minutes. A solution of allyl bromide (491 mg) in tetrahydrofuran (2.5 ml) was

added dropwise therein and the resultant mixture was stirred under the same conditions for 2 hours and 30 minutes. After addition of a saturated aqueous solution of ammonium chloride under the same conditions, the reaction mixture was extracted with ethyl acetate. The extract was washed successively with 1N hydrochloric acid, brine, and a saturated aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent : toluene - ethyl acetate) over silica gel to afford 2-allyl-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran 1,1-dioxide (419 mg) as a colorless oil.

IR (Film) : 1639, 1311, 1243, 1126 cm^{-1}

NMR ($CDCl_3$, δ) : 1.81-1.86 (2H, m), 2.09-2.21 (3H, m), 2.53-2.68 (1H, m), 2.86-3.09 (2H, m), 3.17-3.35 (2H, m), 5.02-5.09 (1H, m), 5.14-5.31 (2H, m), 6.94-7.05 (4H, m), 7.31 (2H, d, J=9.0Hz), 7.61 (2H, d, J=9.0Hz)

(+) API-ES MS m/z : 399 and 401 (M^++Na)

Preparation 1-6)

1.5M Solution of lithium diisopropylamide mono tetrahydrofuran in cyclohexane (0.34 ml) was added dropwise to a stirred solution of 2-allyl-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran 1,1-dioxide (162 mg) in tetrahydrofuran (2.5 ml) under a nitrogen atmosphere and dry ice - acetone cooling and the resultant solution was stirred under the same conditions for 35 minutes. A solution of methyl iodide (134 mg) in tetrahydrofuran (0.5 ml) was added dropwise therein and the resultant mixture was stirred under the same condition for 1 hour and 20 minutes. After addition of a saturated aqueous solution of ammonium chloride under the same conditions, the reaction mixture was extracted with ethyl acetate. The extract was washed successively with 1N hydrochloric acid and brine, dried over sodium sulfate, and evaporated in vacuo.

The residue was chromatographed (eluent : toluene - ethyl acetate) over silica gel (8.1 g) to afford 2-allyl-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-6-methyl-2H-thiopyran 1,1-dioxide (78 mg) as a paste.

IR (KBr) : 1639, 1284, 1244, 1126 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38 (3H, d, J=6.7Hz), 1.82-2.25 (5H, m), 2.61 (1H, m), 2.99 (1H, dd,=14.3, 7.7Hz), 3.32-3.39 (2H, m), 5.02-5.08 (1H, m), 5.16-5.29 (2H, m), 6.95-7.03 (4H, m), 7.28-7.33 (2H, m), 7.57-7.64 (2H, m)

(+) APCI MS m/z : 391 and 393 (M^++H)

Preparation 2

2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran (148 mg) was prepared from 3,4,5,6-tetrahydro-2-(4-hydroxyphenyl)-2H-thiopyran (292 mg) and 4-chloroiodobenzene (430 mg) in a similar manner to that of Preparation 1-3).

mp : 69.5-70.5°C

Preparation 3

2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran (97 mg) was prepared from tetrahydro-2H-thiopyran (510 mg) and 4-bromo-4'-chlorodiphenyl ether (2.12 g) in a similar manner to that of Preparation 1-1).

mp : 69.5-70.5°C

Preparation 4-1)

5-Chlorovaleryl chloride (17.1 g) was added dropwise to a stirred suspension of aluminum chloride (14.7 g) in dichloromethane (125 ml) under a nitrogen atmosphere and ice cooling over 5 minutes and the resulting solution was stirred under the same conditions for 10 minutes, then therein a solution of 4-chlorodiphenyl ether (20.5 g) in dichloromethane (115 ml) was added dropwise over 20 minutes. The resulting mixture was stirred under the same conditions

for 1 hour and 15 minutes, and poured into a mixture of 7% hydrochloric acid and ice. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The oily residue was powdered from n-hexane to afford 4-(5-chlorovaleryl)-4'-chlorodiphenyl ether (30.9 g) as a colorless powder.

mp : 59.5-60.5°C

IR (KBr) : 1672, 1250 cm^{-1}

NMR ($CDCl_3$, δ) : 1.85-1.91 (4H, m), 2.94-3.02 (2H, m), 3.55-3.62 (2H, m), 6.96-7.05 (4H, m), 7.36 (2H, d, J=9.0Hz), 7.95 (2H, d, J=8.9Hz)

(+) API-ES MS m/z : 345, 347 and 349 (M^++Na)

Preparation 4-2)

A solution of sodium borohydride (2.16 g) in water (59 ml) was added dropwise to a stirred suspension of 4-(5-chlorovaleryl)-4'-chlorodiphenyl ether (30.8 g) and sodium bicarbonate (9.61 g) in ethanol (480 ml) under a nitrogen atmosphere at room temperature over 10 minutes and the resulting mixture was stirred under the same conditions for 3 hours. After removal of ethanol, the reaction mixture was acidified with 3N hydrochloric acid (70 ml) and extracted with toluene. The extract was washed successively with water, a saturated aqueous solution of sodium bicarbonate, and brine, dried over sodium sulfate, and evaporated in vacuo to afford 4-(5-chloro-1-hydroxypentyl)-4'-chlorodiphenyl ether (31.1 g) as a yellow oil.

IR (Film) : 3383 (br), 1242 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43-1.89 (7H, m), 3.53 (2H, t, J=6.6Hz), 4.67 (1H, m), 6.89-7.01 (4H, m), 7.24-7.34 (4H, m)

(+) API-ES MS m/z : 347, 349 and 351 (M^++Na), 311 and 313 (M^+-HCl+Na)

Preparation 4-3)

Thionyl chloride (31.2 g) was added dropwise to a stirred solution of 4-(5-chloro-1-hydroxypentyl)-4'-chlorodiphenyl ether (31.0 g) in chloroform (383 ml) under ice cooling and the resulting solution was stirred under reflux for 4 hours. The reaction mixture was cooled to room temperature and evaporated in vacuo. The residue was partitioned between toluene and water. The organic layer was separated, washed with a saturated aqueous solution of sodium bicarbonate (twice) and brine, dried over sodium sulfate, and evaporated in vacuo to afford 4-chloro-4'-(1,5-dichloropentyl)diphenyl ether (33.7 g) as a pale brown oil.

IR (Film) : 1242 cm^{-1}

NMR ($CDCl_3$, δ) : 1.47-1.85 (4H, m), 2.02-2.19 (2H, m), 3.53 (2H, t, J=6.5Hz), 4.85 (1H, dd, J=7.9, 6.6Hz), 6.91-7.00 (4H, m), 7.27-7.38 (4H, m)

Preparation 4-4)

Sodium sulfide nonahydrate (21.8 g) was added gradually to a stirred solution of 4-chloro-4'-(1,5-dichloropentyl)-diphenyl ether (24.0 g) in N,N-dimethylformamide (DMF, 240 ml) under ice cooling and a nitrogen atmosphere, and the resulting mixture was stirred under the same conditions for 2 hours and at room temperature for 3 days, then the reaction mixture was filtered. The filtrate was concentrated in vacuo and partitioned between water and toluene. The organic layer was separated, washed twice with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent: n-hexane - toluene) over silica gel to afford 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran (13.8 g) as a colorless powder.

mp : 69.5-70.5°C

Preparation 5-1)

5-(4-Chlorophenyl)-2-(5-chlorovaleryl)thiophene (3.75 g)

was obtained in a similar manner to that of Preparation 4-1).

NMR ($CDCl_3$, δ) : 1.86-1.95 (4H, m), 2.95 (2H, dd, J=6.9, 6.9Hz), 3.59 (2H, dd, J=6.9, 6.9Hz), 7.30 (1H, d, J=3.9Hz), 7.39 (2H, d, J=8.4Hz), 7.58 (2H, d, J=8.4Hz), 7.67 (1H, d, J=3.9Hz)

Preparation 5-2)

Ethyl 7-chloro-3-[5-(4-chlorophenyl)-2-thienyl]hept-2-enoate (4.2 g) was obtained in a similar manner to that of Preparation 8-2).

NMR ($CDCl_3$, δ) : 1.21-1.34 (3H, m), 1.61-1.93 (4H, m), 2.53-2.57 (1H, m), 3.06-3.11 (1H, m), 3.52-3.60 (2H, m), 4.12-4.23 (2H, m), 5.88 (0.5H, s), 6.23 (0.5H, s), 7.21-7.34 (4H, m), 7.51-7.53 (2H, m)

Preparation 6-1)

Potassium tert-butoxide (1.34 g) was gradually added to a stirred solution of 4-chloro-4'-(1,5-dichloropentyl)-diphenyl ether (3.44 g) and thiobenzoic acid (1.66 g) in N,N-dimethylformamide (48 ml) under ice cooling and a nitrogen atmosphere over 5 minutes, and the resulting mixture was stirred at the same temperature for 2 hours and at room temperature for 16 hours. The reaction mixture was partitioned between ethyl acetate and an aqueous solution of sodium bicarbonate. The organic layer was separated, washed with a saturated aqueous solution of sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated in vacuo. The oily residue (4.63 g) was chromatographed (eluent : n-hexane - toluene) over silica gel to afford 4-(1-benzoylthio-5-chloropentyl)-4'-chlorodiphenyl ether (1.16 g) as a pink oil.

IR (Film) : 1660, 1242 cm^{-1}

NMR ($CDCl_3$, δ) : 1.36-1.65 (2H, m), 1.75-1.90 (2H, m), 1.99-2.12 (2H, m), 3.52 (2H, t, J=6.6Hz), 4.77 (1H, t, J=7.8Hz), 6.90-6.98 (4H, m), 7.25-7.57 (7H,

m), 7.90-7.96 (2H, m)

(+) API-ES MS m/z : 467, 469 and 471 (M^++Na)

Preparation 6-2)

28% Solution of sodium methoxide in methanol (96.5 mg) was added dropwise to a stirred solution of 4-(1-benzoylthio-5-chloropentyl)-4'-chlorodiphenyl ether (223 mg) in methanol (1.1 ml) and acetonitrile (1.1 ml) under ice cooling and the resulting mixture was stirred at the same temperature for 2 hours, then additional 28% solution of sodium methoxide in methanol (96.5 mg), methanol (1.0 ml) and sodium iodide (7.5 mg) were added therein and the mixture was stirred at room temperature for 15 hours. The reaction mixture was acidified with 3N hydrochloric acid (0.5 ml) under ice cooling. The acidic mixture was extracted with toluene. The extract was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue (197 mg) was chromatographed (eluent : n-hexane - toluene) over silica gel (3.9 g) to afford 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran (114 mg) as a colorless powder.

mp : 69.5-70.5°C

Preparation 7-1)

4-(4-Chlorobutyryl)-4'-chlorodiphenyl ether (6.12 g) was prepared from 4-chlorobutyryl chloride (3.10 g) and 4-chlorodiphenyl ether (4.09 g) in a similar manner to that of Preparation 4-1).

IR (Film) : 1680, 1250 cm^{-1}

NMR ($CDCl_3$, δ) : 2.22 (2H, m), 3.14 (2H, t, J=7.0Hz), 3.68 (2H, t, J=6.2Hz), 6.96-7.05 (4H, m), 7.31-7.40 (2H, m), 7.93-8.01 (2H, m)

Preparation 7-2)

4-(4-Chloro-1-hydroxybutyl)-4'-chlorodiphenyl ether (6.14 g) was prepared in a similar manner to that of

Preparation 4-2).

NMR ($CDCl_3$, δ) : 1.76-2.01 (4H, m), 3.51-3.64 (2H, m), 4.70 (1H, m), 6.90-7.00 (4H, m), 7.24-7.34 (4H, m)

(+) API-ES MS m/z : 333, 335 and 337 (M^++Na)

Preparation 7-3)

4-Chloro-4'-(1,4-dichlorobutyl)diphenyl ether (5.75 g) was prepared in a similar manner to that of Preparation 4-3).

IR (Film) : 1244 cm^{-1}

NMR ($CDCl_3$, δ) : 1.72-2.30 (4H, m), 3.57 (2H, t, J=6.4Hz), 4.88 (1H, t, J=7.2Hz), 6.89-7.00 (4H, m), 7.24-7.39 (4H, m)

(+) API-ES MS m/z : 293 and 295 (M^+-Cl)

Preparation 7-4)

2-[4-(4-Chlorophenoxy)phenyl]-2,3,4,5-tetrahydrothiophene (3.63 g) was prepared in a similar manner to that of Preparation 4-4).

IR (Film) : 1238 cm^{-1}

NMR ($CDCl_3$, δ) : 1.87-2.02 (2H, m), 2.23-2.44 (2H, m), 2.99-3.17 (2H, m), 4.50 (1H, dd, J=8.4, 6.0Hz), 6.88-6.97 (4H, m), 7.23-7.31 (2H, m), 7.38 (2H, d, J=8.5Hz)

Preparation 7-5)

2-[4-(4-Chlorophenoxy)phenyl]-2,3,4,5-tetrahydrothiophene 1,1-dioxide (3.05 g) was prepared in a similar manner to that of Preparation 1-4).

mp : 74.5-78.5°C

IR (Film) : 1315, 1234, 1169, 1126 cm^{-1}

NMR ($CDCl_3$, δ) : 2.18-2.55 (4H, m), 3.12-3.36 (2H, m), 4.14 (1H, dd, J=11.7, 7.3Hz), 6.92-7.05 (4H, m), 7.28-7.39 (4H, m)

(+) APCI MS m/z : 323 and 325 (M^++H)

Preparation 8-1)

To a suspension of aluminum chloride (3.58 g) in methylene chloride (20 ml) was added a solution of 5-chlorovaleryl chloride (4.17 g) in methylene chloride (5 ml) dropwise at 0°C. After being stirred for 30 minutes at the same temperature, a solution of 4-chlorodiphenyl ether (6 g) in methylene chloride (5 ml) was added therein and the mixture was stirred under ice-bath cooling for 2 hours. After 4N hydrochloric acid was added carefully to decompose excess aluminum chloride, the organic layer was separated and the aqueous layer was extracted with chloroform (20 ml x 2). The combined organic layer was washed with water and brine, and concentrated under reduced pressure. The resulting residue was washed with hexane to give 4-(5-chlorovaleryl)-4'-chlorodiphenyl ether (6.89 g) as a slightly yellow solid.

NMR (DMSO-d_6, δ) : 1.84-1.95 (4H, m), 2.99 (2H, t, J=7Hz), 3.42 (2H, t, J=7Hz), 6.99 (2H, d, J=9Hz), 7.00 (2H, d, J=9Hz), 7.37 (2H, d, J=9Hz), 7.96 (2H, d, J=9Hz)

Preparation 8-2)

To a suspension of sodium hydride (60% oil dispersion, 3.14 g) in tetrahydrofuran (160 ml) was added a solution of triethyl phosphonoacetate (5.23 ml) in tetrahydrofuran (20 ml) at 0°C. After being stirred 30 minutes at the same temperature, a solution of 4-(5-chlorovaleryl)-4'-chlorodiphenyl ether (48 g) in tetrahydrofuran (60 ml) was added therein, and the reaction mixture was refluxed overnight. The mixture was cooled to room temperature, poured into water, and concentrated under reduced pressure. The residue was extracted with ethyl acetate (200 ml x 3). The combined extract was washed with brine, dried over magnesium sulfate and concentrated to give ethyl 7-chloro-3-[4-(4-chlorophenoxy)phenyl]hept-2-enoate (E:Z = 1:1 mixture) (67.4 g) as a yellow oil.

NMR ($CDCl_3$, δ) : 1.14 (1.5H, t, J=7Hz), 1.26 (1.5H, t, J=7Hz), 1.29-1.40 (2H, m), 1.50-1.67 (2H, m), 1.74-1.89 (2H, m), 2.45 (1.5H, t, J=7Hz), 3.09 (1.5H, t, J=7Hz), 3.51 (1H, t, J=7Hz), 3.53 (1H, t, J=7Hz), 4.03 (1H, q, J=7Hz), 4.14 (1H, q, J=7Hz), 5.89 (0.5H, s), 6.04 (0.5H, s), 6.90-7.01 (4H, m), 7.14 (2H, d, J=8Hz), 7.28 (1H, d, J=8Hz), 7.30 (1H, d, J=8Hz), 7.42 (2H, d, J=8Hz)

Preparation 8-3)

A solution of sodium iodide (128 g) and ethyl 7-chloro-3-[4-(4-chlorophenoxy)phenyl]hept-2-enoate (67.4 g) in acetone (200 ml) was refluxed for 24 hours. The resulting mixture was poured into water (300 ml) and extract with ethyl acetate (100 ml x 2). The combined organic layer was washed with water and brine, and dried over magnesium sulfate to give ethyl 3-[4-(4-chlorophenoxy)phenyl]-7-iodo-hept-2-enoate (67.8 g) (E:Z = 1:1 mixture) as a yellow oil.

NMR ($CDCl_3$, δ) : 1.14 (1.5H, t, J=7Hz), 1.26 (1.5H, t, J=7Hz), 1.29-1.37 (2H, m), 1.46-1.62 (2H, m), 1.78-1.94 (2H, m), 2.44 (1.5H, t, J=7Hz), 3.12 (1.5H, t, J=7Hz), 3.18 (3H, t, J=7Hz), 4.04 (1H, q, J=7Hz), 4.20 (1H, q, J=7Hz), 5.88 (0.5H, s), 6.04 (0.5H, s), 6.89-7.00 (4H, m), 7.14 (2H, d, J=8Hz), 7.26-7.36 (3H, m), 7.42 (2H, d, J=8Hz)

Preparation 8-4)

A mixture of ethyl 3-[4-(4-chlorophenoxy)phenyl]-7-iodo-hept-2-enoate (59.8 g) and thiourea (9.39 g) in ethanol (123 ml) was refluxed for 24 hours. The resulting mixture was cooled and evaporated to give ethyl 7-amidinothio-3-[4-(4-chlorophenoxy)phenyl]hept-2-enoate hydroiodide (70.2 g) (E:Z = 1:1 mixture) as slightly yellow oil.

NMR (DMSO-d_6, δ) : 1.05 (1.5H, t, J=7Hz), 1.24 (1.5H, t, J=7Hz), 1.33-1.68 (4H, m), 2.48 (1H, t, J=7Hz),

3.05-3.16 (3H, m), 3.96 (1H, q, J=7Hz), 4.12 (1H, q, J=7Hz), 5.93 (0.5H, s), 6.07 (0.5H, s), 6.96-7.13 (4H, m), 7.20 (1H, d, J=8Hz), 7.46 (1H, d, J=8Hz), 7.48 (1H, d, J=8Hz), 7.60 (1H, d, J=8Hz)

MS (ES-) m/z : 433 (M-H)

Preparation 9-1)

4-(5-Chlorovaleryl)-4'-fluorodiphenyl ether (3.86 g) was obtained in a similar manner to that of Preparation 4-1).

NMR ($CDCl_3$, δ) : 1.81-1.92 (4H, m), 2.97 (2H, dd, J=7, 7Hz), 3.53-3.6 (2H, m), 6.94-7.12 (6H, m), 7.92-7.95 (2H, m)

Preparation 9-2)

Ethyl 7-chloro-3-[4-(4-fluorophenoxy)phenyl]hept-2-enoate (1.90 g) was obtained in a similar manner to that of Preparation 8-2).

NMR ($CDCl_3$, δ) : 1.31 (3H, dd, J=7, 7Hz), 1.54-1.64 (2H, m), 1.78-1.88 (2H, m), 3.12 (2H, dd, J=7.5, 7.5Hz), 3.53 (2H, dd, J=7, 7Hz), 4.20 (2H, ddd, J=7, 7, 7Hz), 6.03 (1H, s), 6.93-7.09 (6H, m), 7.39-7.42 (2H, m)

Preparation 10-1)

4-(5-Chlorovaleryl)-4'-bromodiphenyl ether (6.71 g) was obtained in a similar manner to that of Preparation 4-1).

NMR ($CDCl_3$, δ) : 1.82-1.94 (4H, m), 2.99 (2H, t, J=6.5Hz), 3.60 (2H, t, J=6.5Hz), 6.95 (2H, d, J=9Hz), 7.00 (2H, d, J=9Hz), 7.51 (2H, d, J=9Hz), 7.95 (2H, d, J=9Hz)

Preparation 10-2

Ethyl 3-[4-(4-bromophenoxy)phenyl]-7-chlorohept-2-enoate (7.55 g) was obtained in a similar manner to that of Preparation 8-2).

NMR ($CDCl_3$, δ) : 1.14 (1.5H, t, J=7Hz), 1.21-1.39 (1.5H, m), 1.49-1.65 (2H, m), 1.74-1.88 (2H, m), 2.47 (1H, t, J=7Hz), 3.12 (1H, t, J=7Hz), 3.47-3.56 (2H, m), 4.03 (1H, q, J=7Hz), 4.20 (1H, q, J=7Hz), 5.89 (0.5H, s), 6.04 (0.5H, s), 6.86-6.99 (4H, m), 7.39-7.50 (4H, m)

Preparation 10-3)

Ethyl 3-[4-(4-bromophenoxy)phenyl]-7-iodohept-2-enoate (7.85 g) was obtained in a similar manner to that of Preparation 8-3).

NMR ($CDCl_3$, δ) : 1.14 (1.5H, t, J=7Hz), 1.21-1.39 (1.5H, m), 1.49-1.65 (2H, m), 1.74-1.88 (2H, m), 2.47 (1H, t, J=7Hz), 3.12 (1H, t, J=7Hz), 3.47-3.56 (2H, m), 4.03 (1H, q, J=7Hz), 4.20 (1H, q, J=7Hz), 5.89 (0.5H, s), 6.04 (0.5H, s), 6.86-6.99 (4H, m), 7.39-7.50 (4H, m)

Preparation 10-4)

Ethyl 7-amidinothio-3-[4-(4-bromophenoxy)phenyl]hept-2-enoate hydroiodide (10.4 g) was obtained in a similar manner to that of Preparation 8-4).

NMR (DMSO-d_6, δ) : 1.06 (1.5H, t, J=7Hz), 1.24 (1.5H, t, J=7Hz), 1.35-1.52 (2H, m), 1.54-1.75 (2H, m), 3.06-3.17 (2H, m), 3.39-3.49 (2H, m), 3.94 (1H, q, J=7Hz), 4.15 (1H, q, J=7Hz), 5.94 (0.5H, s), 6.07 (0.5H, s), 6.96-7.11 (4H, m), 7.56-7.64 (4H, m), 9.01-9.15 (4H, m)

MS (ESI+) m/z : 479, 563 (+TFA)

Preparation 11-1)

Methyl 4-(5-chlorovaleryl)phenyl ether (8.77 g) was obtained in a similar manner to that of Preparation 4-1).

NMR ($CDCl_3$, δ) : 1.84-1.94 (4H, m), 2.97 (2H, t, J=7Hz), 3.59 (2H, t, J=6.5Hz), 3.88 (3H, s), 6.94

(2H, d, J=9Hz), 7.95 (2H, d, J=9Hz)

Preparation 11-2)

To a stirred solution of lithium diisopropylamide in tetrahydrofuran (prepared from diisopropylamine (2.32 g) and n-butyl lithium (14.3 ml, 1.6M in n-hexane) in tetrahydrofuran (14 ml) was added dropwise ethyl acetate (2.80 g) while maintaining -60°C on a dry-ice acetone bath. The mixture was stirred for 1 hour at -60°C and quenched by addition of saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate. The obtained organic phase was washed with saturated aqueous ammonium chloride three times and brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluted with 5 to 10% ethyl acetate in n-hexane) to give ethyl 7-chloro-3-hydroxy-3-(4-methoxyphenyl)-heptanoate (3.56 g) as an oil.

NMR ($CDCl_3$, δ) : 1.12 (3H, t, J=7.5Hz), 1.16-1.30 (1H, m), 1.39-1.56 (1H, m), 1.62-1.82 (4H, m), 2.77 (1H, d, J=16Hz), 2.94 (1H, d, J=16Hz), 3.45 (2H, t, J=6.5Hz), 3.80 (3H, s), 4.04 (2H, q, J=7.5Hz), 4.38 (1H, s), 6.86 (2H, d, J=9Hz), 7.31 (2H, d, J=9Hz)

Preparation 11-3)

A mixture of ethyl 7-chloro-3-hydroxy-3-(4-methoxyphenyl)heptanoate (3.55 g), potassium thioacetate (1.42 g) and catalytic amount of tetrabutyl ammonium iodide ($n\text{-}Bu_4NI$) (150 mg) in N,N-dimethylformamide (30 ml) was stirred for 6 hours at room temperature. The mixture was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic phase was washed with saturated aqueous ammonium chloride three times and brine, dried over sodium sulfate and evaporated in vacuo to give ethyl 7-acetylthio-3-hydroxy-3-(4-methoxyphenyl)heptanoate (3.61 g) as an oil.

NMR ($CDCl_3$, δ) : 1.12 (3H, t, J=7Hz), 1.33-1.55 (4H, m), 1.66-1.80 (2H, m), 2.30 (3H, s), 2.72-2.81 (3H, m), 2.93 (1H, d, J=15.5Hz), 3.80 (3H, s), 4.03 (2H, q, J=7Hz), 4.36 (1H, s), 6.85 (2H, d, J=9Hz), 7.30 (2H, d, J=9Hz)

Preparation 11-4)

A mixture of ethyl 7-acetylthio-3-hydroxy-3-(4-methoxyphenyl)heptanoate (3.60 g) and potassium carbonate (1.40 g) in ethanol (54 ml) was stirred for 6 hours at room temperature and concentrated in vacuo. The residue was partitioned between ethyl acetate and 1% aqueous citric acid. The separated organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo to give ethyl 3-hydroxy-3-(4-methoxyphenyl)-7-mercaptoheptanoate (3.01 g) as an oil.

NMR ($CDCl_3$, δ) : 1.12 (3H, t, J=7.5Hz), 1.26 (1H, t, J=7.5Hz), 1.35-1.60 (4H, m), 1.65-1.82 (2H, m), 2.40-2.57 (2H, m), 2.77 (1H, d, J=16Hz), 2.94 (1H, d, J=16Hz), 3.80 (3H, s), 4.04 (2H, q, J=7.5Hz), 4.36 (1H, s), 6.86 (2H, d, J=9Hz), 7.30 (2H, d, J=9Hz)

Preparation 12-1)

5-(4-Fluorophenyl)-2-(5-chlorovaleryl)thiophene (2.03 g) was obtained in a similar manner to that of Preparation 4-1).

NMR ($CDCl_3$, δ) : 1.79-1.99 (4H, m), 2.95 (2H, t, J=7Hz), 3.59 (2H, t, J=7Hz), 7.12 (2H, dd, J=8, 8Hz), 7.59-7.68 (4H, m)

Preparation 12-2)

Ethyl 7-chloro-3-[5-(4-fluorophenyl)-2-thienyl]hept-2-enoate (1.71 g) (E:Z = 1:1 mixture) was obtained in a similar manner to that of Preparation 8-2).

NMR ($CDCl_3$, δ) : 1.24 (1.5H, t), 1.37 (1.5H, t), 1.63-

1.98 (4H, m), 2.56 (0.5H, t, J=7Hz), 2.87-3.00 (1H, m), 3.08 (0.5H, t, J=7Hz), 3.53 (1H, t, J=7Hz), 3.61 (1H, t, J=7Hz), 4.10-4.24 (2H, m), 5.87 (0.5H, s), 6.22 (0.5H, s), 7.04-7.31 (3H, m), 7.55-7.69 (3H, m)

Preparation 12-3)

Ethyl 3-[5-(4-fluorophenyl)-2-thienyl]-7-iodohept-2-enoate (1.94 g) was obtained in a similar manner to that of Preparation 8-3).

NMR ($CDCl_3$, δ) : 1.06 (1.5H, t, J=7Hz), 1.32 (1.5H, t, J=7Hz), 1.67-2.08 (4H, m), 3.24 (2H, t, J=7Hz), 4.18 (2H, q, J=7Hz), 6.22 (1H, s), 6.92-7.30 (4H, m), 7.48-7.60 (2H, m)

Preparation 12-4)

Ethyl 7-amidinothio-3-[5-(4-fluorophenyl)-2-thienyl]hept-2-enoate hydroiodide (1.57 g) was obtained in a similar manner to that of Preparation 8-4).

NMR ($CDCl_3$, δ) : 1.05 (3H, t, J=7Hz), 1.57-1.82 (4H, m), 3.18 (2H, t, J=7Hz), 4.14 (2H, q, J=7Hz), 4.36 (2H, t, J=7Hz), 6.19 (1H, s), 7.24-7.69 (6H, m)

MS (ES+) m/z = 407 (M+H)

Preparation 13-1)

4-(5-Chlorovaleryl)biphenyl (1.35 g) was obtained in a similar manner to that of Preparation 4-1).

NMR ($CDCl_3$, δ) : 1.90-1.93 (4H, m), 3.06 (2H, dd, J=6, 6Hz), 3.61 (2H, dd, J=7, 7Hz), 7.40-7.50 (3H, m), 7.63 (2H, d, J=8Hz), 7.69 (2H, d, J=8Hz), 8.03 (2H, d, J=8Hz)

Preparation 13-2)

Ethyl 3-(4-biphenylyl)-7-chlorohept-2-enoate (1 g) was obtained in a similar manner to that of Preparation 8-2).

NMR ($CDCl_3$, δ) : 1.10 (1.5H, dd, J=7, 7Hz), 1.33 (1.5H, dd, J=7, 7Hz), 1.55-1.68 (1H, m), 1.76-1.90 (1H, m), 2.51 (1H, dd, J=7.5, 7.5Hz), 3.18 (1H, dd, J=7.5, 7.5Hz), 3.52 (1H, dd, J=6.5, 6.5Hz), 3.54 (1H, dd, J=6.5, 6.5Hz), 4.02 (1H, ddd, J=7, 7, 7Hz), 4.22 (1H, ddd, J=7, 7, 7Hz), 5.92 (0.5H, s), 6.13 (0.5H, s), 7.24-7.65 (9H, m)

Preparation 14-1)

4'-Chloro-4-(5-chlorovaleryl)biphenylyl (3.29 g) was obtained in a similar manner to that of Preparation 4-1).

NMR ($CDCl_3$, δ) : 1.90-1.93 (4H, m), 3.05 (2H, dd, J=6, 6Hz), 3.60 (2H, dd, J=6, 6Hz), 7.44 (2H, d, J=8Hz), 7.56 (2H, d, J=8Hz), 7.65 (2H, d, J=8Hz), 8.03 (2H, d, J=8Hz)

Preparation 14-2)

Ethyl 7-chloro-3-(4'-chloro-4-biphenylyl)hept-2-enoate (0.70 g) was obtained in a similar manner to that of Preparation 8-2).

NMR ($CDCl_3$, δ) : 1.11 (1.5H, dd, J=7, 7Hz), 1.32 (1.5H, dd, J=7, 7Hz), 1.50-1.58 (1H, m), 1.58-1.65 (1H, m), 2.49 (1H, dd, J=7, 7Hz), 3.17 (1H, dd, J=7, 7Hz), 3.50 (1H, dd, J=6, 6Hz), 3.54 (1H, dd, J=6, 6Hz), 4.01 (1H, ddd, J=7, 7, 7Hz), 4.22 (1H, ddd, J=7, 7, 7Hz), 5.93 (0.5H, s), 6.12 (0.5H, s), 7.40-7.58 (8H, m)

Preparation 15-1)

4'-Bromo-4-(5-chlorovaleryl)biphenyl (1.97 g) was obtained in a similar manner to that of Preparation 4-1).

NMR ($CDCl_3$, δ) : 1.90-1.93 (4H, m), 3.05 (2H, dd, J=7, 7Hz), 3.60 (2H, dd, J=6, 6Hz), 7.49 (2H, d, J=8Hz), 7.60 (2H, d, J=8Hz), 7.65 (2H, d, J=8Hz), 8.03 (2H, d, J=8Hz)

Preparation 15-2)

Ethyl 7-chloro-3-(4'-bromo-4-biphenylyl)hept-2-enoate (0.64 g) was obtained in a similar manner to that of Preparation 8-2).

NMR ($CDCl_3$, δ) : 1.11 (1.5H, dd, J=7, 7Hz), 1.33 (1.5H, dd, J=7, 7Hz), 1.52-1.67 (2H, m), 1.75-1.89 (2H, m), 2.50 (1H, dd, J=7, 7Hz), 3.17 (1H, dd, J=8, 8Hz), 3.51 (1H, dd, J=7, 7Hz), 3.54 (1H, dd, J=7, 7Hz), 4.02 (1H, ddd, J=7, 7, 7Hz), 4.22 (1H, ddd, J=7, 7, 7Hz), 5.93 (0.5H, s), 6.11 (0.5H, s), 7.24-7.60 (8H, m)

Preparation 16-1)

4'-Fluoro-4-(5-chlorovaleryl)biphenyl (2.95 g) was obtained in a similar manner to that of Preparation 4-1).

NMR ($CDCl_3$, δ) : 1.89-1.95 (4H, m), 3.05 (2H, dd, J=7, 7Hz), 3.60 (2H, dd, J=6, 6Hz), 7.13-7.19 (2H, m), 7.57-7.65 (2H, m), 8.03 (2H, d, J=8.4Hz)

Preparation 16-2)

Ethyl 7-chloro-3-(4'-fluoro-4-biphenylyl)hept-2-enoate (1.07 g) was obtained in a similar manner to that of Preparation 8-2).

NMR ($CDCl_3$, δ) : 1.33 (3H, dd, J=7, 7Hz), 1.59-1.67 (2H, m), 1.81-1.90 (2H, m), 3.17 (2H, dd, J=7.5, 7.5Hz), 3.54 (2H, dd, J=7, 7Hz), 4.22 (2H, ddd, J=7, 7, 7Hz), 6.12 (1H, s), 7.14 (2H, dd, J=8, 8Hz), 7.50-7.59 (6H, m)

Preparation 17)

Methyl 3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide (844 mg) was obtained in a similar manner to that of Preparation 1-4).

mp : 78-82°C

NMR ($CDCl_3$, δ) : 1.44-1.80 (3H, m), 1.83-1.96 (1H, m),

2.10-2.42 (2H, m), 2.72-2.85 (1H, m), 3.14-3.78 (1H, m), 5.57 (1H, dd, J=3, 8Hz), 3.82 (3H, s)

MS (ESI-) m/z : 191 (M-H)

Preparation 18)

To a solution of potassium ethyl malonate (16.7 g) in acetonitrile (4 ml) was added triethylamine (15.1 g) and magnesium chloride (11.1 g) at 0°C and the reaction mixture was stirred at ambient temperature for 2.5 hours. To the resulting slurry was added phenoxybenzoyl chloride (10.86 g) [prepared from 4-phenoxybenzoic acid (10 g) and thionyl chloride (20 ml)] dropwise over 25 minutes at 0°C and the reaction mixture was stirred at ambient temperature for 5 hours. After the reaction mixture was concentrated in vacuo, toluene and 13% aqueous hydrochloric acid (60 ml) was added therein cautiously while keeping the temperature below 25°C. The organic layer was washed with 13% aqueous hydrochloric acid and concentrated in vacuo to give ethyl 3-oxo-3-(4-phenoxyphenyl)propanoate as a yellow oil (14 g).

NMR ($CDCl_3$, δ) : 1.27 (3H, t, J=7.0Hz), 3.95 (2H, s), 4.24 (2H, q, J=7.0Hz), 6.99 (2H, d, J=8.0Hz), 7.07 (2H, d, J=8.0Hz), 7.18 (1H, dd, J=8.0, 8.0Hz), 7.41 (2H, dd, J=8.0, 8.0Hz), 7.92 (2H, d, J=8.0Hz)

MS (ESI) m/z : 283.1 (M-H)

Preparation 19-1)

5-Bromo-2-(5-chlorovaleryl)thiophene (13.4 g) was obtained in a similar manner to that of Preparation 4-1).

NMR ($CDCl_3$, δ) : 1.86-1.91 (4H, m), 2.88 (2H, dd, J=6.9, 6.9Hz), 3.55 (2H, dd, J=6.6, 6.6Hz), 7.11 (1H, d, J=4.2Hz), 7.45 (1H, d, J=4.2Hz)

Preparation 19-2)

Ethyl 7-chloro-3-(5-bromo-2-thienyl)hept-2-enoate (12.5 g) was obtained in a similar manner to that of Preparation 8-

2).

NMR ($CDCl_3$, δ) : 1.22-1.59 (3H, m), 1.65-1.92 (4H, m), 3.01-3.06 (1H, m), 3.50-3.59 (2H, m), 4.10-4.23 (2H, m), 5.85 (0.5H, s), 6.09 (0.5Hz, s), 6.98-7.07 (2H, m)

Example 1

1.5M Lithium diisopropylamide mono tetrahydrofuran in cyclohexane (0.28 ml) was added dropwise to a stirred suspension of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran 1,1-dioxide (117 mg) in tetrahydrofuran (2.4 ml) under dry ice - acetone cooling and a nitrogen atmosphere, and the mixture was stirred under the same conditions for 15 minutes, then a solution of tert-butyl bromoacetate (75 mg) in tetrahydrofuran (0.2 ml) was added dropwise therein and the resulting mixture was stirred under the same conditions for 2 hours. A saturated aqueous solution of ammonium chloride was added to the stirred reaction mixture and the resulting mixture was extracted with diethyl ether. The extract was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent : toluene - ethyl acetate) over silica gel to afford a mixture (86 mg) of t-butyl 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetate 1,1-dioxide and the starting material.

A solution of trifluoroacetic acid (560 mg) and the obtained mixture (79 mg) in dichloromethane (3.0 ml) was allowed to stand at room temperature for 3 days and evaporated in vacuo. The residue was dissolved in ethyl acetate and extracted five times with a saturated aqueous solution of sodium bicarbonate. The aqueous extracts were combined, acidified with hydrochloric acid, and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, and evaporated in vacuo to afford 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-

thiopyran-2-acetic acid 1,1-dioxide (44 mg) as a colorless powder.

mp : 191-193°C

IR (KBr) : 1711, 1290, 1244, 1124 cm^{-1}

NMR ($CDCl_3$, δ) : 1.75-2.05 (2H, m), 2.15 (2H, m), 2.6-2.85 (2H, m), 3.08-3.15 (2H, m), 3.21 (1H, d, J=15.6Hz), 3.60 (1H, d, J=15.6Hz), 6.94-7.01 (4H, m), 7.31 (2H, dd, J=6.7, 2.1Hz), 7.59 (2H, d, J=9.0Hz)

(-) API-ES MS m/z : 393 (M^+-H)

Anal. Calcd. for $C_{19}H_{19}ClO_5S$: C 57.79, H 4.85

Found : C 57.88, H 4.83

Example 2

A mixture of ethyl 2-(4-methoxyphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetate (100 mg) and lithium hydroxide monohydrate (42.8 mg) in a mixture of methanol and water was stirred for 4 hours at 60°C. After cooling to room temperature, the mixture was acidified with 4N hydrochloric acid and concentrated in vacuo. The residue was partitioned between ethyl acetate and 1N hydrochloric acid. The separated organic layer was washed with brine, dried over sodium sulfate and evaporated in vacuo to give 2-(4-methoxyphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (93 mg) as a crystalline solid.

NMR (DMSO-d_6, δ) : 1.44-1.80 (4H, m), 2.26-2.54 (3H, m), 2.62-2.79 (2H, m), 3.00 (1H, d, J=14.5Hz), 3.75 (3H, s), 6.89 (2H, d, J=9Hz), 7.48 (2H, d, J=9Hz)

MS (ESI-) m/z : 265

Example 3

To a solution of ethyl 2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetate (315 mg) in methanol (4 ml) was added 1N sodium hydroxide aqueous solution (1.3 ml) at 0°C and the mixture was stirred for 5

hours at room temperature. The resulting mixture was evaporated to remove methanol. The residue was acidified with 1N hydrochloric acid (HCl) and extracted with ethyl acetate (x3). The combined organic layer was washed with brine, dried over magnesium sulfate and concentrated to give 2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (296 mg) as white solid.

NMR ($CDCl_3$, δ) : 1.58-1.92 (4H, m), 2.20-2.32 (1H, m), 2.57-2.68 (2H, m), 2.70-2.81 (1H, m), 2.89 (1H, d, J=14Hz), 2.97 (1H, d, J=14Hz), 6.97-7.08 (4H, m), 7.48-7.56 (2H, m)

MS (ES-) m/z : 335 (M-H)

Example 4

To a solution of methyl 2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide in methanol (MeOH) (5 ml) was added solution of lithium hydroxide monohydrate (375 mg) in water (H_2O) (5 ml) at room temperature. After being stirred at 60°C for 2 hours, the mixture was concentrated in vacuo to remove MeOH. The residual solution was acidified by 1M hydrochloric acid and extracted with ethyl acetate (AcOEt) (20 ml x 2). The combined extract was washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give 2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylic acid 1,1-dioxide (320 mg) as an amorphous powder.

NMR ($CDCl_3$, δ) : 1.70-1.84 (2H, m), 1.95-2.20 (3H, m), 2.25-2.37 (1H, m), 3.11-3.25 (3H, m), 3.16 (1H, d, J=14Hz), 6.91 (2H, d, J=8Hz), 7.00 (2H, d, J=8Hz), 7.11 (1H, t, J=8Hz), 7.20 (2H, d, J=8Hz), 7.33 (2H, t, J=8Hz)

MS (ESI-) m/z : 359 (M-H)

Example 5

2-(4-Phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-

carboxylic acid (280 mg) was obtained in a similar manner to that of Example 4.

NMR ($CDCl_3$, δ) : 1.45-2.02 (5H, m), 2.35-2.46 (1H, m), 2.52-2.65 (1H, m), 2.68-2.85 (1H, m), 3.07 (2H, dd, J=3, 14Hz), 6.90 (2H, d, J=8Hz), 6.99 (2H, d, J=8Hz), 7.09 (1H, t, J=8Hz), 7.13 (2H, d, J=8Hz), 7.32 (2H, t, J=8Hz)

MS (ESI-) m/z : 327 (M-H)

Example 6

To a solution of ethyl 2-(4-phenoxyphenyl)-1,3-dithiane-2-acetate (370 mg) in ethanol (4 ml) was added 1N sodium hydroxide aqueous solution (2 ml) and the mixture was stirred at 50°C for 3 hours. The resulting mixture was evaporated to remove ethanol. The residue was acidified with 1N HCl and extracted with diethyl ether. The organic layer was washed with brine, and dried over magnesium sulfate. The solvent was evaporated to give 2-(4-phenoxyphenyl)-1,3-dithiane-2-acetic acid (280 mg) as white crystal.

NMR ($CDCl_3$, δ) : 2.03 (2H, br), 2.83 (4H, br), 3.22 (2H, br), 6.93-7.05 (4H, m), 7.13 (1H, d, J=7.0Hz), 7.41-7.48 (2H, m), 7.82-7.86 (2H, m)

MS (ESI) m/z : 345.1 (M-H)

Example 7

1.5M Solution of lithium diisopropylamide mono-tetrahydrofuran in cyclohexane (1.60 ml) was added dropwise to a stirred solution of 2-[4-(4-chlorophenoxy)phenyl]-2,3,4,5-tetrahydrothiophene 1,1-dioxide (646 mg) in tetrahydrofuran (6.5 ml) under a nitrogen atmosphere and dry ice - acetone cooling, and the resultant solution was stirred under the same conditions for 35 minutes. A solution of allyl bromide (532 mg) in tetrahydrofuran (1.9 ml) was added dropwise therein and the resultant mixture was stirred under the same conditions for 1 hour and 30 minutes. After addition of a

saturated aqueous solution of ammonium chloride (10 ml) under the same conditions, the reaction mixture was extracted with ethyl acetate. The extract was washed successively with 1N hydrochloric acid and a saturated aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and evaporated in vacuo to afford an oil (0.68 g).

Potassium permanganate (259 mg), sodium periodate (1.75 g), and potassium carbonate (618 mg) was successively added to a stirred emulsion of the obtained oil in tert-butyl alcohol (22 ml) and water (38 ml) at room temperature and the resulting mixture was stirred at the same temperature for 1 hour and 40 minutes. The reaction mixture was acidified to pH c.a. 1.0 with 1N hydrochloric acid (10 ml) under ice cooling, and then sodium bisulfite was added portionwise therein under the same condition till the mixture became yellow. The yellow mixture was extracted with ethyl acetate. The extract was washed with an aqueous solution of sodium bisulfite and brine, dried over sodium sulfate, and evaporated in vacuo. The powdery residue was washed with a mixture of diisopropyl ether - diethyl ether to afford a colorless powder (401 mg), 388 mg of which was chromatographed (eluent : toluene - ethyl acetate - acetic acid) over silica gel to afford an oil. The obtained oil was powdered from n-hexane to afford 2-[4-(4-chlorophenoxy)phenyl]-2,3,4,5-tetrahydrothiophene-2-acetic acid 1,1-dioxide (306 mg) as a colorless amorphous powder.

mp : 45-50°C

IR (KBr) : 2750-2400, 1734, 1716, 1300, 1244, 1126 cm^{-1}

NMR (DMSO-d_6, δ) : 2.16-2.25 (2H, m), 2.65-2.77 (2H, m), 3.08-3.41 (4H, m), 7.00-7.10 (4H, m), 7.41-7.51 (4H, m), 12.38 (1H, br)

(-) API-ES MS m/z : 379 and 381 (M^+-H)

Anal. Calcd. for $C_{18}H_{17}ClO_5S$: C 56.76, H 4.50

Found : C 57.32, H 5.04

Example 8

Potassium permanganate (172 mg), sodium periodate (1.28 g), and potassium carbonate (409 mg) was successively added to a stirred emulsion of 2-allyl-2-[4-(4-chlorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran 1,1-dioxide (372 mg) in tert-butyl alcohol (15 ml) and water (26 ml) at room temperature and the resulting mixture was stirred at the same temperature for 1 hour and 30 minutes. The reaction mixture was acidified to pH c.a. 1.0 with conc. hydrochloric acid under ice cooling, and then sodium bisulfite was added portionwise therein under the same condition till the mixture became yellow. The yellow mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatogrphed (eluent : toluene - ethyl acetate - acetic acid) over silica gel to afford a colorless powder (277 mg), which was washed with n-hexane to afford 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (250 mg) as a colorless powder.

mp : 191-193°C

Example 9

2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-6-methyl-2H-thiopyran-2-acetic acid 1,1-dioxide (59 mg) was prepared in a similar manner to that of Example 8.

IR (KBr) : 3442, 1735, 1714, 1284, 1245, 1124 cm^{-1}

NMR (DMSO-d_6, δ) : 1.16 (3H, d, J=6.6Hz), 1.62-1.98 (4H, m), 2.47-2.63 (2H, m), 3.2-3.59 (3H, m), 6.98-7.10 (4H, m), 7.46 (2H, d, J=9.0Hz), 7.55 (2H, d, J=9.0Hz)

(-) API-ES MS m/z : 407 and 409 (M^+-H)

Example 10

A suspension of (2R or 2S)-2-[4-(4-chlorophenoxy)-phenyl]-3,4,5,6-tetrahydro-N-((1R)-1-phenylethyl)-2H-

thiopyran-2-acetamide 1,1-dioxide (diastereomer A, 149 mg) obtained in Example 31 in a mixture of 14N sulfuric acid (7.0 ml) and 1,4-dioxane (4.2 ml) was stirred under reflux for 21 hours and cooled to room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine (twice), dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent : dichloromethane - methanol) over silica gel to afford (2R or 2S)-(-)-2-[4-(4-chlorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (an optical isomer A, 109 mg) as a crude brown gum.

IR (KBr) : 1734, 1716, 1284, 1244, 1122 cm^{-1}

NMR ($CDCl_3$, δ) : 1.93 (2H, m), 2.14 (2H, m), 2.6-2.85 (2H, m), 3.08-3.16 (2H, m), 3.22 (1H, d, J=15.6Hz), 3.62 (1H, d, J=15.6Hz), 6.95-7.04 (4H, m), 7.28-7.35 (2H, m), 7.60 (2H, d, J=9.0Hz)

(-) API-ES MS m/z : 393 and 395 (M^+-H)

$[\alpha]_D^{25}$: -32.3° (C=1.0, MeOH)

Analytical chiral HPLC :

column : Chiralpak AS (4.6 x 250 mm, Daicel Chemical Industries, Ltd.)

eluent : n-hexane-ethanol-TFA (700:300:1)

flow rate : 1.0 ml/minute

detection : 220 nm

retention time : 50.0 minutes

Example 11

(2R or 2S)-2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (an optical isomer B, 77 mg) was prepared from (2R or 2S)-(+)-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-N-((1R)-1-phenylethyl)-2H-thiopyran-2-acetamide 1,1-dioxide (diastereomer B, 133 mg) obtained in Example 31 in a similar manner to that of Example 10.

IR (KBr) : 1711, 1290, 1242, 1122 cm^{-1}

NMR ($CDCl_3$, δ) : 1.82-1.95 (2H, m), 2.10-2.15 (2H, m), 2.62-2.80 (2H, m), 3.03-3.11 (2H, m), 3.21 (1H, d, J=15.6Hz), 3.60 (1H, d, J=15.6Hz), 6.92-7.01 (4H, m), 7.28-7.34 (2H, m), 7.59 (2H, d, J=9.0Hz)

(-) API-ES MS m/z : 393 (M^+-H)

Analytical chiral HPLC :

column : Chiralpak AS (4.6 x 250 mm, Daicel Chemical Industries, Ltd.)

eluent : n-hexane-ethanol-TFA (700:300:1)

flow rate : 1.0 ml/minute

detection : 220 nm

retention time : 8.96 minutes

Example 12

To a solution of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (16.8 g) in ethyl acetate (420 ml) was added (R)-(+)-α-methylbenzylamine (2.84 g) at room temperature. After being stirred overnight at the same temperature, the resulting crystal was filtrated and washed with ethyl acetate to give (2R or 2S)-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (R)-(+)-α-methylbenzylamine salt (9.43 g). A suspension of resulting salt in ethyl acetate (200 ml) was washed with 1N hydrochloric acid (100 ml x 2), water and brine, and concentrated to give the free acid. This procedure was repeated three times (second:amine 0.75 eq; third:0.85 eq) to give the optically resoluted (2R or 2S)-(-)-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (an optical isomer A) (4.75 g) as a white solid.

$[\alpha]_D^{25}$: -32.3° (C=1.0, MeOH)

Optical purity : 91% ee

Analytical chiral HPLC :

column : Chiralpak AS (4.6 x 250 mm, Daicel Chemical Industries, Ltd.)

eluent : n-hexane-ethanol-TFA (700:300:1)
flow rate : 1.0 ml/minutes
detection : 220 nm
retention time : 50.0 minutes

Example 13

To a solution of 2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (1 g) in ethanol (8 ml) was added (R)-(+)-α-methylbenzylamine (185 mg) at room temperature. After being stirred overnight at the room temperature, the resulting crystal was filtrated and washed with ethanol to give 2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (R)-(+)-α-methylbenzylamine salt. A suspension of resulting salt in ethyl acetate was washed with 1N hydrochloric acid and brine, and concentrated to give the free acid. This procedure was repeated two times to give the optically resoluted (2R or 2S)-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (300 mg) as a white solid.

NMR (DMSO-d_6, δ) : 1.74-1.87 (4H, m), 2.30-2.37 (1H, m), 3.07-3.56 (5H, m), 7.02 (1H, d, J=4.2Hz), 7.21 (1H, d, J=4.2Hz)
MS (ESI-) m/z : 351 (M-H)
$[\alpha]_D^{25}$: -25.3° (C=1.0, MeOH)
Optical purity : 95% ee
Analytical chiral HPLC :
column : Chiralpak AS (4.6 x 250 mm, Daicel Chemical Industries, Ltd.)
eluent : n-hexane-ethanol-trifluoroacetic acid (TFA) (700:300:1)
flow rate : 1.0 ml/minute
detection: 220 nm
retention time : 20.2 minutes

Example 14

A mixture of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (98.7 mg), ammonium formate (78.8 mg), and 10% palladium - carbon (50% wet, 60 mg) in ethanol (5 ml) was stirred under reflux for 3 hours and 20 minutes, and filtered. The filtrate was evaporated in vacuo and the residue was partitioned between ethyl acetate and 0.1N hydrochloric acid. The organic layer was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was powdered from diisopropyl ether to afford 3,4,5,6-tetrahydro-2-(4-phenoxyphenyl)-2H-thiopyran-2-acetic acid 1,1-dioxide (87 mg) as a colorless powder.

mp : 208.5-209.5°C

IR (KBr) : 2750-2550, 1707, 1290, 1246, 1124 cm^{-1}

NMR ($CDCl_3$, δ) : 1.75-2.25 (4H, m), 2.74 (2H, m), 3.11 (2H, m), 3.21 (1H, d, J=15.6Hz), 3.61 (1H, d, J=15.6Hz), 6.97-7.07 (4H, m), 7.14 (1H, t, J=7.4Hz), 7.36 (2H, t, J=7.7Hz), 7.59 (2H, d, J=9.0Hz)

(-) API-ES MS m/z : 359 (M^+-H)

Example 15

A solution of oxalyl chloride (76.2 mg) in dichloromethane (0.7 ml) was added dropwise to a stirred suspension of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (118 mg) and N,N-dimethylformamide (1.10 mg) in dichloromethane (1.2 ml) under ice cooling and a nitrogen atmosphere, then the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 2 hours and evaporated in vacuo. The residue was dissolved in dichloromethane (1.6 ml) and the solution was added dropwise to a stirred mixture of hydroxylammonium chloride (125 mg), 1N aqueous solution of sodium hydroxide (1.8 ml), tetrahydrofuran (3.6 ml), and tert-butyl alcohol (1.8 ml) at room temperature and the

resulting mixture was stirred at room temperature for 2 hours and 30 minutes. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent : toluene - ethyl acetate - acetic acid) over silica gel (2.6 g) to afford a colorless powder, which was washed with diisopropyl ether to afford 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-N-hydroxy-2H-thiopyran-2-acetamide 1,1-dioxide (88 mg) as a colorless powder.

mp : 179-180°C (dec.)

IR (KBr) : 3421, 3315, 3220, 1652, 1284, 1248, 1119 cm^{-1}

NMR (DMSO-d_6, δ) : 1.74-1.99 (4H, m), 2.5 (1H, m), 2.87 (1H, br d, J=13.8Hz), 3.01-3.55 (4H, m), 6.87-7.12 (4H, m), 7.42-7.59 (4H, m), 8.73 (1H, s), 10.48 (1H, s)

(+) API-ES MS m/z : 432 (M^++Na)

Anal. Calcd. for $C_{19}H_{20}ClNO_5S$: C 55.68, H 4.92, N 3.42

Found : C 55.67, H 5.28, N 3.23

Example 16

A solution of oxalyl chloride (55.8 mg) in dichloromethane (0.5 ml) was added dropwise to a stirred solution of crude (2R or 2S)-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (an optical isomer A, 87 mg) obtained in Example 12 and N,N-dimethylformamide (0.80 mg) in dichloromethane (0.88 ml) under ice cooling and a nitrogen atmosphere, then the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 2 hours and 30 minutes, and evaporated in vacuo. The residue was dissolved in dichloromethane (0.9 ml) and the solution was added dropwise to a stirred mixture of hydroxylammonium chloride (91.7 mg), 1N aqueous solution of sodium hydroxide (1.3 ml),

tetrahydrofuran (2.6 ml), and tert-butyl alcohol (1.3 ml) at room temperature and the resulting mixture was stirred at the same temperature for 1 hour and 30 minutes. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent : toluene - ethyl acetate - acetic acid) over silica gel (1.9 g) to afford a pale brown powder (67 mg), which was washed with diisopropyl ether to afford (R or S)-(-)-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-N-hydroxy-2H-thiopyran-2-acetamide 1,1-dioxide (optical isomer A, 55 mg) as a colorless powder.

mp : 183.5-187°C (dec.)

$[\alpha]_D^{28}$: -9.3° (C=0.71, MeOH)

IR (KBr) : 3446, 3423, 1653, 1284, 1250, 1119 cm^{-1}

NMR (DMSO-d_6, δ) : 1.75-2.05 (4H, m), 2.5 (1H, m), 2.87 (1H, br d, J=12.9Hz), 3.01-3.5 (4H, m), 7.00 (2H, d, J=8.9Hz), 7.08 (2H, d, J=8.9Hz), 7.46 (2H, d, J=8.9Hz), 7.56 (2H, d, J=8.9Hz), 8.73 (1H, s), 10.48 (1H, s)

(+) API-ES MS m/z : 432 and 434 (M^++Na)

(-) API-ES MS m/z : 408 and 410 (M^+-H)

Analytical chiral HPLC :

column : Chiralpak AS (4.6 x 250 mm, Daicel Chemical Industries, Ltd.)

eluent : n-hexane-ethanol-TFA (700:300:1)

flow rate : 1.0 ml/minute

detection : 220 nm

retention time : 18.2 minutes

Example 17

(R or S)-(+)-2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-N-hydroxy-2H-thiopyran-2-acetamide 1,1-dioxide (41 mg) was prepared from crude (2R or 2S)-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-

acetic acid 1,1-dioxide (an optical isomer B, 87 mg) obtained in Example 11 in a similar manner to that of Example 16.

mp : 187-188°C (dec.)

$[\alpha]_D^{28}$: 10.5° (C=0.56, MeOH)

IR (KBr) : 3444, 3423, 3317, 3224, 1655, 1284, 1250, 1122 cm^{-1}

NMR (DMSO-d_6, δ) : 1.75-2.05 (4H, m), 2.5 (1H, m), 2.87 (1H, br d, J=13.6Hz), 3.01-3.52 (4H, m), 7.00 (2H, d, J=8.9Hz), 7.08 (2H, d, J=8.9Hz), 7.46 (2H, d, J=8.9Hz), 7.56 (2H, d, J=8.9Hz), 8.73 (1H, s), 10.48 (1H, s)

(+) API-ES MS m/z : 432 and 434 (M^++Na)

(-) API-ES MS m/z : 408 and 410 (M^+-H)

Analytical chiral HPLC :

column : Chiralpak AS (4.6 x 250 mm, Daicel Chemical Industries, Ltd.)

eluent : n-hexane-ethanol-TFA (700:300:1)

flow rate : 1.0 ml/minute

detection : 220 nm

retention time : 27.9 minutes

Example 18

2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-N-hydroxy-6-methyl-2H-thiopyran-2-acetamide 1,1-dioxide (30 mg) was prepared from 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-6-methyl-2H-thiopyran-2-acetic acid 1,1-dioxide (55 mg) in a similar manner to that of Example 15.

mp : 102°C (dec.)

IR (KBr) : 3446 and 3421 (br), 1668, 1282, 1246, 1124 cm^{-1}

NMR (DMSO-d_6, δ) : 1.17 (3H, d, J=6.6Hz), 1.5-2.05 (4H, m), 2.4 (1H, m), 2.8-2.95 (1H, br d), 3.09 (1H, d, J=15.0Hz), 3.23 (1H, d, J=15.0Hz), 3.54 (1H, m), 7.00 (2H, d, J=8.8Hz), 7.08 (2H, d, J=8.9Hz), 7.42-7.49 (2H, m), 7.56 (2H, d, J=8.9Hz), 8.73 (1H, s),

10.49 (1H, s)

(+) API-ES MS m/z : 446 and 448 (M^++Na)

Example 19

3,4,5,6-Tetrahydro-N-hydroxy-2-(4-phenoxyphenyl)-2H-thiopyran-2-acetamide 1,1-dioxide (41 mg) was prepared from 3,4,5,6-tetrahydro-2-(4-phenoxyphenyl)-2H-thiopyran-2-acetic acid 1,1-dioxide (66 mg) in a similar manner to that of Example 15.

mp : 182-183°C (dec.)

IR (KBr) : 3446 and 3423 (br), 1655, 1288, 1246, 1115 cm^{-1}

NMR (DMSO-d_6, δ) : 1.75-2.05 (4H, m), 2.4 (1H, m), 2.87 (1H, br d, J=13.0Hz), 3.04-3.55 (4H, m), 6.96 (2H, d, J=8.9Hz), 7.06 (2H, d, J=7.5Hz), 7.19 (1H, t, J=7.3Hz), 7.43 (2H, t, J=7.4Hz), 7.54 (2H, d, J=8.9Hz), 8.74 (1H, s), 10.48 (1H, s)

(+) APCI MS m/z : 376 (M^++H), 343 (M^+-NHOH)

(-) API-ES MS m/z : 374 (M^+-H)

Example 20

2-[4-(4-Chlorophenoxy)phenyl]-2,3,4,5-tetrahydro-N-hydroxy-2-thiophene-2-acetamide 1,1-dioxide (88 mg) was prepared from 2-[4-(4-chlorophenoxy)phenyl]-2,3,4,5-tetrahydrothiophene-2-acetic acid 1,1-dioxide (122 mg) in a similar manner to that of Example 15.

mp : 63-68°C (dec.)

IR (KBr) : 3423 (br), 1662, 1296, 1244, 1126 cm^{-1}

NMR (DMSO-d_6, δ) : 2.19-2.23 (2H, m), 2.56-3.28 (6H, m), 6.99-7.10 (4H, m), 7.38-7.48 (4H, m), 8.73 (1H, s), 10.40 (1H, s)

(+) APCI MS m/z : 396 and 398 (M^++H), 363 and 365 (M^+-NHOH)

Anal. Calcd. for $C_{18}H_{18}ClNO_5S$: C 54.61, H 4.58, N 3.54

Found : C 55.20, H 5.06, N 3.26

Example 21

To a solution of potassium hydroxide (400 g) in water (200 ml) was added a solution of ethyl 7-amidinothio-3-[4-(4-chlorophenoxy)phenyl]hept-2-enoate hydroiodide (70.1 g) in tetrahydrofuran (100 ml), and the mixture was refluxed overnight. After the solution was cooled and acidified with 1N HCl, the mixture was extracted with ethyl acetate (100 ml x 3). The combined organic layer was washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure to give 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (60 g) as an yellow oil.

NMR ($CDCl_3$, δ) : 1.51-1.90 (4H, m), 2.26-2.38 (1H, m), 2.48-2.68 (3H, m), 2.90 (2H, d, J=14Hz), 2.98 (2H, d, J=14Hz), 6.94 (4H, d, J=8Hz), 7.27 (2H, d, J=8Hz), 7.57 (2H, d, J=8Hz)

MS (ES-) m/z : 361 (M-H)

Example 22

2-[4-(4-Bromophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (3.99 g) was obtained in a similar manner to that of Example 21.

NMR ($CDCl_3$, δ) : 1.50-1.87 (4H, m), 2.27-2.49 (1H, m), 2.47-2.70 (3H, m), 2.90 (1H, d, J=15Hz), 3.00 (1H, d, J=15Hz), 6.96 (4H, d, J=9Hz), 7.44 (4H, d, J=9Hz)

MS (ESI-) m/z : 407

Example 23

Ethyl 2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetate (117 mg) was obtained from 7-amidinothio-3-[5-(4-fluorophenyl)-2-thienyl]hept-2-enoate hydroiodide in a similar manner to that of Example 21.

NMR ($CDCl_3$, δ) : 1.12 (3H, t, J=7Hz), 1.49-1.92 (4H,

m), 2.18-2.30 (1H, m), 2.55-2.68 (2H, m), 2.73-2.82 (1H, m), 2.81 (1H, d, J=14Hz), 2.89 (1H, d, J=14Hz), 4.01 (2H, q, J=7Hz), 6.93-7.11 (4H, m), 7.49-7.56 (2H, m)

Example 24

To a solution of ethyl 3-(4-biphenylyl)-7-chlorohept-2-enoate (0.90 g) in acetone (15 ml) was added NaI (1.55 g) at 60°C. After being stirred overnight, the reaction mixture was cooled, concentrated in vacuo, diluted with water, and extracted with ether. The ether extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. A mixture of this residue and thiourea (158 mg) in ethanol (EtOH) (15 ml) was refluxed with stirring for 24 hours. The resulting mixture was cooled and concentrated in vacuo to yield the isothiouronium salt. To a solution of potassium hydroxide (KOH) (1.74 g) in water was added this isothiouronium salt, and the mixture was refluxed with stirring for 8 hours. The reaction mixture was cooled at 0°C and was quenched by cautions dropwise addition of a solution of 50% aqueous sulfuric acid (H_2SO_4) until acidic. The mixture was extracted with ether, and the organic layers were washed with water and brine, dried over magnesium sulfate ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent : 5% methanol (MeOH) in chloroform ($CHCl_3$) to give 2-(4-biphenylyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (335 mg) as an amorphous.

NMR ($CDCl_3$, δ) : 1.60-1.85 (4H, m), 2.30-2.39 (1H, m), 2.50-2.70 (3H, m), 2.94 (1H, d, J=14.7Hz), 3.01 (1H, d, J=14.7Hz), 7.34 (1H, dd, J=7, 7Hz), 7.56-7.61 (4H, m), 7.68-7.71 (2H, m)

MS (ESI-) m/z : 311 (M-H)

Example 25

2-[4-(4-Fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (200 mg) was obtained in a similar manner to that of Example 24.

NMR ($CDCl_3$, δ) : 1.60-1.84 (4H, m), 2.27-2.36 (1H, m), 2.50-2.67 (3H, m), 2.88 (1H, d, J=15Hz), 2.97 (1H, d, J=16Hz), 6.91 (2H, d, J=9Hz), 6.99-7.06 (4H, m), 7.56 (2H, d, J=9Hz)

MS (ESI-) m/z : 345 (M-H)

Example 26

2-[4-(4-Chlorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (310 mg) was obtained in a similar manner to that of Example 24.

NMR ($CDCl_3$, δ) : 1.60-1.85 (4H, m), 2.29-2.38 (1H, m), 2.52-2.69 (3H, m), 2.94 (1H, d, J=14.7Hz), 3.01 (1H, d, J=14.7Hz), 7.39 (2H, d, J=8Hz), 7.50-7.54 (4H, m), 7.69 (2H, d, J=8Hz)

MS (ESI-) m/z : 345 (M-H)

Example 27

2-[4-(4-Bromophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (120 mg) was obtained in a similar manner to that of Example 24.

NMR ($CDCl_3$, δ) : 1.61-1.85 (4H, m), 2.29-2.36 (1H, m), 2.51-2.69 (3H, m), 2.94 (1H, d, J=14.7Hz), 3.01 (1H, d, J=14.7Hz), 7.45 (2H, d, J=9Hz), 7.51-7.57 (4H, m), 7.69 (2H, d, J=9Hz)

MS (ESI-) m/z : 389 (M-H)

Example 28

2-[4-(4-Fluorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (200 mg) was obtained in a similar manner to that of Example 24.

NMR ($CDCl_3$, δ) : 1.60-1.85 (4H, m), 2.29-2.38 (1H, m), 2.53-2.67 (2H, m), 2.94 (1H, d, J=15Hz), 3.01 (1H,

d, J=16Hz), 7.07-7.12 (2H, m), 7.51-7.56 (4H, m), 7.69 (2H, d, J=8.5Hz)

MS (ESI-) m/z : 329 (M-H)

Example 29

2-[5-(4-Chlorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (2.5 g) was obtained in a similar manner to that of Example 24.

NMR (DMSO-d_6, δ) : 1.55-1.75 (4H, m), 2.25-2.32 (1H, m), 2.45-2.63 (3H, m), 2.74 (1H, d, J=14Hz), 3.97 (1H, d, J=14Hz), 7.02 (1H, d, J=3.6Hz), 7.40 (1H, d, J=3.6Hz), 7.45 (2H, d, J=8.7Hz), 7.64 (2H, d, J=8.7Hz)

MS (ESI-) m/z : 351 (M-H)

Example 30

2-(5-Bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (8.5 g) was obtained in a similar manner to that of Example 24.

NMR (DMSO-d_6, δ) : 1.45-1.73 (4H, m), 2.12-2.20 (1H, m), 2.45-2.70 (4H, m), 2.87 (1H, d, J=14.4Hz), 6.84 (1H, d, J=4.2Hz), 7.08 (1H, d, J=4.2Hz)

Example 31

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSCD) hydrochloride (205 mg) was added to a stirred mixture of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (326 mg), (R)-(+)-α-methylbenzylamine (105 mg), and 1-hydroxybenzotriazole (123 mg) in dichloromethane (8 ml) under ice cooling, and then the resulting mixture was stirred at the same temperature for 2 hours and at room temperature for 2 hours and extracted with dichloromethane. The extract was washed successively with water, 0.1N hydrochloric acid, water, and a saturated aqueous solution of sodium bicarbonate, dried over magnesium sulfate,

and evaporated in vacuo. The residue was chromatographed (eluent : toluene - ethyl acetate) over silica gel to afford diastereomer A (180 mg) and diastereomer B (181 mg) of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-[N-[(1R)-1-phenylethyl)]acetamide 1,1-dioxide as a colorless solid and colorless crystals, respectively.

Diastereomer A :

mp : 138-160.5°C

$[\alpha]_D^{27}$: 31.0° (C=0.52, MeOH)

IR (KBr) : 3421 (br), 1651, 1288, 1244, 1124 cm^{-1}

NMR ($CDCl_3$, δ) : 1.06 (3H, d, J=6.8Hz), 1.94-2.15 (4H, m), 2.68-2.74 (2H, m), 2.99-3.26 (4H, m), 4.72-4.87 (1H, m), 5.21 (1H, br d, J=8.0Hz), 6.97 (2H, d, J=9.0Hz), 7.00-7.11 (4H, m), 7.19-7.37 (5H, m), 7.70 (2H, d, J=9.0Hz)

(+) APCI MS m/z : 498 and 500 (M^++H)

Diastereomer B :

mp : 82.5-89°C

$[\alpha]_D^{27}$: 53.4° (C=0.50, MeOH)

IR (KBr) : 3365 (br), 1651, 1288, 1246, 1122 cm^{-1}

NMR ($CDCl_3$, δ) : 1.32 (3H, d, J=6.9Hz), 1.91 (2H, m), 2.13 (2H, m), 2.62 (2H, m), 2.99-3.30 (4H, m), 4.85 (1H, m), 5.31 (1H, br d, J=8.0Hz), 6.74-6.80 (2H, m), 6.90-6.99 (4H, m), 7.15-7.36 (5H, m), 7.58 (2H, d, J=9.0Hz)

(+) APCI MS m/z : 498 and 500 (M^++H)

Example 32

To a solution of (2R or 2S)-2-[4-(4-chlorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (4.75 g) obtained in Example 10, O-(2-tetrahydropyranyl)hydroxylamine (2.11 g), and 1-hydroxybenzotriazole (1.95 g) in N,N-dimethylformamide (60 ml) was added WSCD hydrochloride (2.77 g). After being

stirred for 4 hours at room temperature, the solvent was evaporated in vacuo, and the resulting residue was dissolved in ethyl acetate (60 ml). The solution was washed with 5% aqueous citric acid solution, saturated sodium bicarbonate solution and brine, and dried over magnesium sulfate. The solution was concentrated under reduced pressure to give (2R or 2S)-N-(2-tetrahydropyranyloxy)-2-[4-(4-chlorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (6.52 g) as a slightly yellow oil.

NMR ($CDCl_3$, δ) : 1.46-2.22 (10H, m), 2.77 (1H, br), 3.02-3.28 (4H, m), 3.38-3.55 (1H, m), 3.65-3.78 (1H, m), 4.37 (0.5H, s), 4.77 (0.5H, s), 6.95 (2H, d, J=8Hz), 7.00 (2H, d, J=8Hz), 7.29 (2H, d, J=8Hz), 7.65 (2H, d, J=8Hz), 8.28 (1H, br)

MS (ES-) m/z : 493 (M-H)

The following compounds were obtained in a similar manner to that of Example 32.

Example 33

2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (140 mg)

NMR ($CDCl_3$, δ) : 1.42-1.91 (10H, m), 2.23-2.36 (1H, m), 2.49-2.72 (4H, m), 2.74-2.83 (1H, m), 3.45-3.58 (1H, m), 3.71-3.83 (1H, m), 4.55 (1H, s), 4.79 (0.5H, s), 6.89-7.03 (4H, m), 7.27 (2H, d, J=8Hz), 7.60 (2H, d, J=8Hz), 7.96 (0.5H, s), 8.16 (0.5H, s)

MS (ES-) m/z : 460 (M-H)

Example 34

N-(2-Tetrahydropyranyloxy)-2-[4-(4-fluorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (307 mg)

NMR ($CDCl_3$, δ) : 1.53-1.70 (10H, m), 2.08-2.17 (2H, m), 2.73-2.76 (2H, m), 3.02-3.23 (4H, m), 3.42-3.52

(1H, m), 6.98-7.05 (6H, m), 7.64 (2H, d, J=9Hz)

MS (ESI-) m/z : 476 (M-H)

Example 35

N-(2-Tetrahydropyranyloxy)-2-[4-(4-fluorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (250 mg)

NMR ($CDCl_3$, δ) : 1.50-1.64 (6H, m), 1.74-1.78 (4H, m), 2.25-2.34 (2H, m), 2.52-2.70 (4H, m), 2.76-2.82 (1H, m), 3.49-3.57 (1H, m), 3.72-3.83 (1H, m), 6.95-7.04 (6H, m), 7.59 (2H, d, J=9Hz)

MS (ESI-) m/z : 444 (M-H)

Example 36

N-(2-Tetrahydropyranyloxy)-2-[4-(4-fluorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1-oxide (152 mg)

NMR ($CDCl_3$, δ) : 1.54-1.81 (10H, m), 2.45-2.56 (2H, m), 2.75-2.96 (5H, m), 3.53-3.59 (1H, m), 3.81-3.87 (1H, m), 6.95-7.04 (6H, m), 7.39 (2H, d, J=9Hz)

MS (ESI-) m/z : 460 (M-H)

Example 37

N-(2-Tetrahydropyranyloxy)-2-[4-(4-fluorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (173 mg)

NMR ($CDCl_3$, δ) : 1.45-1.75 (6H, m), 1.89-2.01 (2H, m), 2.06-2.20 (2H, m), 2.68-2.80 (2H, m), 3.00-3.24 (4H, m), 3.40-3.55 (1H, m), 3.64-3.75 (1H, m), 4.49 (0.5H, br s), 4.75 (0.5H, br s), 6.93 (2H, d, J=9Hz), 7.04 (2H, d, J=9Hz), 7.45 (2H, d, J=9Hz), 7.67 (2H, d, J=9Hz), 7.77 (2H, d, J=9Hz), 7.77 (0.5H, br s), 7.90 (0.5H, br s)

MS (ESI-) m/z : 536

Example 38

N-(2-Tetrahydropyranyloxy)-2-[4-[4-(4-fluorophenyl)-phenoxy]phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (122 mg)

NMR ($CDCl_3$, δ) : 1.45-1.79 (6H, m), 1.88-2.02 (2H, m), 2.06-2.24 (2H, m), 2.66-2.82 (2H, m), 3.00-3.25 (4H, m), 3.40-3.56 (1H, m), 3.64-3.77 (1H, m), 4.41 (0.5H, br s), 4.75 (0.5H, br s), 7.00-7.18 (6H, m), 7.42-7.56 (4H, m), 7.67 (2H, d, J=9Hz), 7.75 (0.5H, br s), 7.89 (0.5H, br s)

MS (ESI-) m/z : 552

Example 39

N-(2-Tetrahydropyranyloxy)-2-(4-methoxyphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (113 mg)

NMR ($CDCl_3$, δ) : 1.41-1.72 (6H, m), 1.87-2.01 (2H, m), 2.06-2.21 (2H, m), 2.59-2.81 (2H, m), 3.00-3.25 (4H, m), 3.32-3.73 (2H, m), 3.81 (3H, s), 4.37-4.44 (0.5H, m), 4.69-4.79 (0.5H, m), 6.91-7.03 (2H, m), 7.53-7.69 (2H, m), 7.70-7.91 (1H, m)

MS (ESI-) m/z : 396

Example 40

N-(2-Tetrahydropyranyloxy)-2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (145 mg)

NMR ($CDCl_3$, δ) : 1.45-1.99 (10H, m), 2.17-2.32 (1H, m), 2.50-2.97 (3H, m), 3.40-3.51 (1H, m), 3.71-3.86 (1H, m), 4.70 (0.5H, s), 4.86 (0.5H, s), 6.93-7.19 (4H, m), 7.52-7.67 (2H, m), 8.09 (0.5H, s), 8.22 (0.5H, s)

MS (ES-) m/z : 434 (M-H)

Example 41

N-(2-Tetrahydropyranyloxy)-2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (345 mg)

NMR ($CDCl_3$, δ) : 1.39-1.79 (6H, m), 1.89-2.00 (2H, m), 2.05-2.27 (2H, m), 2.64-2.92 (2H, m), 3.06 (1H, s), 3.09-3.16 (1H, m), 3.27-3.50 (1H, m), 3.61-3.73 (1H, m), 4.53 (0.5H, br s), 4.82 (1H, br s), 7.02-7.11 (2H, m), 7.16-7.27 (2H, m), 7.55 (1H, d, J=8Hz), 7.57 (1H, d, J=8Hz), 7.97 (0.5H, s), 8.13 (1H, br s)

Example 42

N-(2-Tetrahydropyranyloxy)-2-(4-biphenylyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (330 mg)

NMR ($CDCl_3$, δ) : 1.45-1.81 (10H, m), 2.29-2.38 (1H, m), 2.52-2.96 (7H, m), 3.58-3.75 (1H, m), 7.35-7.37 (1H, m), 7.42-7.47 (2H, m), 7.56-7.64 (4H, m), 7.71-7.75 (2H, m)

MS (ESI-) m/z : 410 (M-H)

Example 43

N-(2-Tetrahydropyranyloxy)-2-(4-biphenylyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (390 mg)

NMR ($CDCl_3$, δ) : 1.38-1.66 (6H, m), 1.95-2.03 (2H, m), 2.12-2.21 (2H, m), 2.73-2.84 (2H, m), 2.89 (1H, s), 2.96 (1H, s), 3.04-3.31 (4H, m), 3.50-3.62 (1H, m), 7.35-7.47 (3H, m), 7.58-7.60 (2H, m), 7.65-7.70 (2H, m), 7.77-7.81 (2H, m)

MS (ESI-) m/z : 442 (M-H)

Example 44

N-(2-Tetrahydropyranyloxy)-2-[4-(4-chlorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (300 mg)

NMR ($CDCl_3$, δ) : 1.60-1.66 (6H, m), 1.94-2.03 (2H, m), 2.13-2.21 (2H, m), 2.76-2.84 (2H, m), 2.89-2.96 (2H, m), 3.07-3.27 (4H, m), 3.53-3.65 (1H, m), 7.41 (2H, d, J=8.5Hz), 7.51 (2H, d, J=8.5Hz), 7.60-7.64

(2H, m), 7.76-7.80 (2H, m)

MS (ESI-) m/z : 476 (M-H)

Example 45

N-(2-Tetrahydropyranyloxy)-2-[4-(4-bromophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg)

NMR ($CDCl_3$, δ) : 1.44-1.62 (10H, m), 2.10-2.20 (2H, m), 2.76-2.84 (2H, m), 3.05-3.31 (4H, m), 3.53-3.65 (1H, m), 7.45 (2H, d, J=9Hz), 7.56-7.64 (4H, m), 7.70-7.77 (2H, m)

MS (ESI-) m/z : 520 (M-H)

Example 46

N-(2-Tetrahydropyranyloxy)-2-[4-(4-fluorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (230 mg)

NMR ($CDCl_3$, δ) : 1.45-1.70 (10H, m), 2.12-2.19 (2H, m), 2.79-2.81 (2H, m), 3.05-3.32 (4H, m), 3.55-3.64 (1H, m), 7.13 (2H, dd, J=9, 9Hz), 7.52-7.61 (4H, m), 7.73-7.78 (2H, m)

MS (ESI-) m/z : 460 (M-H)

Example 47

N-(2-Tetrahydropyranyloxy)-2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxamide 1,1-dioxide (360 mg)

NMR ($CDCl_3$, δ) : 1.45-2.31 (12H, m), 2.42-2.63 (1H, m), 3.03-3.20 (3H, m), 3.43 (1H, d, J=14Hz), 3.57-3.70 (1H, m), 3.84-4.02 (1H, m), 4.91, 5.11 (1H, s), 6.91 (2H, d, J=8Hz), 6.97-7.14 (3H, m), 7.19 (2H, t, J=8Hz), 7.28-7.48 (2H, m), 9.99, 10.07 (1H, s)

MS (ESI-) m/z : 458 (M-H)

Example 48

N-(2-Tetrahydropyranyloxy)-2-(4-phenoxybenzyl)-3,4,5,6-

tetrahydro-2H-thiopyran-2-carboxamide (320 mg)

NMR ($CDCl_3$, δ) : 1.33-2.00 (12H, m), 2.47-2.59 (1H, m), 2.64-2.90 (3H, m), 3.08-3.22 (1H, m), 3.50-3.65 (1H, m), 3.75-4.00 (1H, m), 4.70, 4.98 (1H, s), 6.87-7.20 (7H, m), 7.32 (2H, t, J=8Hz), 9.70 (1H, s)

MS (ESI-) m/z : 426 (M-H)

Example 49

N-(2-Tetrahydropyranyloxy)-2-(4-biphenylylmethyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxamide 1,1-dioxide (152 mg)

NMR ($CDCl_3$, δ) : 1.54-2.35 (12H, m), 2.45-2.66 (1H, m), 3.08-3.25 (3H, m), 3.33-3.55 (1H, m), 3.56-3.70 (1H, m), 3.82-4.08 (1H, m), 4.95, 5.14 (1H, s), 7.23-7.36 (3H, m), 7.42 (2H, t, J=8Hz), 7.47-7.67 (4H, m), 10.01, 10.08 (1H, s)

MS (ESI-) m/z : 442 (M-H)

Example 50

N-(2-Tetrahydropyranyloxy)-2-(4-phenoxyphenyl)-1,3-dithiane-2-acetamide (150 mg)

NMR (DMSO-d_6, δ) : 1.47-1.62 (6H, m), 1.85-1.90 (2H, m), 2.73 (2H, s), 2.89 (4H, br), 3.33 (2H, m), 4.57 (1H, s), 6.98 (2H, d, J=8.0Hz), 7.03 (2H, d, J=8.0Hz), 7.16 (1H, dd, J=8.0, 8.0Hz), 7.40 (2H, dd, J=8.0, 8.0Hz), 7.83 (2H, d, J=8.0Hz)

MS (ESI) m/z : 444.1 (M-H)

Example 51

N-(2-Tetrahydropyranyloxy)-2-[5-(4-chlorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (250 mg)

NMR ($CDCl_3$, δ) : 1.45-1.67 (10H, m), 1.90-1.97 (2H, m), 2.67-3.12 (6H, m), 3.62-3.68 (1H, m), 7.24-7.26

(2H, m), 7.35 (2H, d, J=8.7Hz), 7.52 (2H, d, J=8.7Hz)

MS (ESI-) m/z : 482 (M-H)

Example 52

N-(2-Tetrahydropyranyloxy)-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (190 mg)

NMR ($CDCl_3$, δ) : 1.50-2.17 (11H, m), 2.65-3.10 (6H, m), 3.47-3.58 (1H, m), 3.72-3.81 (1H, m), 7.00-7.05 (2H, m)

MS (ESI-) m/z : 450 (M-H)

Example 53

(2R or 2S)-N-(2-Tetrahydropyranyloxy)-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (80 mg) from (2R or 2S) 2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (63 mg) obtained in Example 13

NMR ($CDCl_3$, δ) : 1.50-2.17 (11H, m), 2.65-3.10 (6H, m), 3.47-3.58 (1H, m), 3.72-3.81 (1H, m), 7.00-7.05 (2H, m)

MS (ESI-) m/z : 450 (M-H)

Example 54

To a mixture of (2R or 2S)-N-(2-tetrahydropyranyloxy)-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (6.51 g) obtained in Example 32 in methanol (40 ml) was added 10% hydrogen chloride in methanol (10 ml) at room temperature. After being stirred for 30 minutes, the solution was concentrated. The residue was purified with silica gel column chromatography (eluent : hexane-EtOAc 1:1) to give (2R or 2S)-(-)-N-hydroxy-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (optical isomer A, 4.72 g) as white

crystalline.

$[\alpha]_D^{25}$: -13.7° (C=0.98, MeOH)

Analytical chiral HPLC :

column : Chiralpak AS (4.6 x 250 mm, Daicel Chemical Industries, Ltd.)

eluent : n-hexane-ethanol-TFA (700:300:1)

flow rate : 1.0 ml/minute

detection : 220 nm

retention time : 18.2 minutes

The following compounds were obtained in a similar manner to that of Example 54.

Example 55

N-Hydroxy-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (61 mg)

NMR (DMSO-d_6, δ) : 1.32-1.78 (4H, m), 2.30-2.58 (4H, m), 2.60-2.73 (2H, m), 6.96-7.08 (4H, m), 7.43 (2H, d, J=8Hz), 7.55 (2H, d, J=8Hz), 10.19 (1H, s)

MS (ESI-) m/z : 376 (M-H)

Example 56

N-Hydroxy-2-[4-(4-fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (220 mg)

NMR (DMSO-d_6, δ) : 1.75-2.03 (4H, m), 2.99 (1H, d, J=14Hz), 3.19 (1H, d, J=14Hz), 3.34-3.50 (4H, m), 6.94 (2H, d, J=9Hz), 7.09-7.14 (2H, m), 7.23-7.29 (2H, m), 7.53 (2H, d, J=9Hz), 8.74 (1H, s)

MS (ESI-) m/z : 392 (M-H)

Example 57

N-Hydroxy-2-[4-(4-fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (143 mg)

NMR (DMSO-d_6, δ) : 1.46-1.73 (4H, m), 2.35-2.49 (4H, m), 2.64-2.71 (2H, m), 6.93 (2H, d, J=9Hz), 7.05-

7.09 (2H, m), 7.20-7.26 (2H, m), 7.53 (2H, d, J=9Hz), 8.62 (1H, s), 10.18 (1H, s)

MS (ESI-) m/z : 360 (M-H)

Example 58

N-Hydroxy-2-[4-(4-fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1-oxide (80 mg)

NMR (DMSO-d_6, δ) : 1.47-1.65 (4H, m), 1.95-2.02 (1H, m), 2.25-2.44 (3H, m), 2.57 (1H, d, J=14Hz), 2.70 (1H, d, J=14Hz), 6.96 (2H, d, J=9Hz), 7.07-7.12 (2H, m), 7.22-7.28 (2H, m), 7.40 (2H, d, J=9Hz), 8.64 (1H, s), 10.31 (1H, s)

MS (ESI-) m/z : 376 (M-H)

Example 59

N-Hydroxy-2-[4-(4-bromophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (104 mg)

NMR ($CDCl_3$, δ) : 1.86-1.97 (2H, m), 2.02-2.23 (2H, m), 2.60-2.80 (2H, m), 3.01-3.24 (4H, m), 6.93 (2H, d, J=9Hz), 7.01 (2H, d, J=9Hz), 7.46 (2H, d, J=9Hz), 7.64 (2H, d, J=9Hz)

MS (ESI-) m/z : 452

Example 60

N-Hydroxy-2-[4-[4[(4-fluorophenyl)phenoxy]phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (63 mg)

NMR ($CDCl_3$, δ) : 1.87-2.00 (2H, m), 2.04-2.25 (2H, m), 2.60-2.82 (2H, m), 3.01-3.25 (4H, m), 7.00-7.19 (6H, m), 7.47-7.57 (4H, m), 7.64 (2H, d, J=9Hz)

MS (ESI-) m/z : 468

Example 61

N-Hydroxy-2-(4-methoxyphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (21 mg)

NMR (DMSO-d_6, δ) : 1.70-2.05 (4H, m), 2.39-2.52 (1H, m), 2.81-2.91 (1H, m), 2.95-3.22 (4H, m), 3.26 (3H, s), 6.91 (2H, d, J=9Hz), 7.45 (2H, d, J=9Hz), 8.70 (1H, s), 10.46 (1H, s)

MS (ESI-) m/z : 312

Example 62

N-Hydroxy-2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (87 mg)

NMR ($CDCl_3$, δ) : 1.45-1.85 (4H, m), 2.35-2.74 (4H, m), 2.46 (1H, d, J=14Hz), 2.66 (1H, d, J=14Hz), 7.17-7.33 (3H, m), 7.45 (1H, d, J=3Hz), 7.64-7.77 (2H, m), 8.74 (1H, s)

MS (ES-) m/z : 350 (M-H)

Example 63

N-Hydroxy-2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (286 mg)

NMR ($CDCl_3$, δ) : 1.69-2.07 (4H, m), 2.35-2.48 (2H, m), 2.94-3.54 (4H, m), 7.17-7.33 (3H, m), 7.45 (1H, d, J=3Hz), 7.64-7.77 (2H, m), 8.74 (1H, s)

MS (ES-) m/z : 382 (M-H)

Example 64

N-Hydroxy-2-(4-biphenylyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (230 mg)

NMR (DMSO-d_6, δ) : 1.61-1.79 (4H, m), 2.39-2.56 (2H, m), 2.65-2.75 (3H, m), 2.89 (1H, s), 7.36 (1H, dd, J=7, 7Hz), 7.47 (2H, dd, J=7, 7Hz), 7.64-7.69 (6H, m), 8.63 (1H, s)

MS (ESI-) m/z : 326 (M-H)

Example 65

N-Hydroxy-2-(4-biphenylyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (230 mg)

NMR (DMSO-d_6, δ) : 1.77-2.05 (4H, m), 2.49-2.51 (2H, m), 3.19-3.41 (4H, m), 7.41 (1H, dd, J=7.5, 7.5Hz), 7.49 (2H, dd, J=7.5, 7.5Hz), 7.65-7.71 (6H, m), 8.74 (1H, s)

MS (ESI-) m/z : 358 (M-H)

Example 66

N-Hydroxy-2-[4-(4-chlorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)

NMR (DMSO-d_6, δ) : 1.78-2.04 (4H, m), 2.91-3.10 (2H, m), 3.17-3.36 (4H, m), 7.54 (2H, d, J=9Hz), 7.61-7.69 (4H, m), 7.73 (2H, d, J=9Hz), 8.72 (1H, s)

Example 67

N-Hydroxy-2-[4-(4-bromophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (70 mg)

NMR (DMSO-d_6, δ) : 1.77-2.06 (4H, m), 2.93-3.08 (2H, m), 3.19-3.36 (4H, m), 7.61-7.70 (8H, m), 8.74 (1H, s)

MS (ESI-) m/z : 436 (M-H)

Example 68

N-Hydroxy-2-[4-(4-fluorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (160 mg)

NMR (DMSO-d_6, δ) : 1.77-2.05 (4H, m), 2.93-3.54 (6H, m), 7.31 (2H, dd, J=9, 9Hz), 7.63-7.77 (6H, m), 8.73 (1H, s), 10.53 (1H, s)

MS (ESI-) m/z : 376 (M-H)

Example 69

N-Hydroxy-2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxamide 1,1-dioxide (199 mg)

NMR ($CDCl_3$, δ) : 1.47-2.20 (5H, m), 2.46-2.62 (1H, m), 2.96-3.20 (3H, m), 3.43 (1H, d, J=14Hz), 6.89 (2H, d, J=8Hz), 6.98 (2H, d, J=8Hz), 7.05-7.18 (3H, m),

7.33 (2H, d, J=8Hz), 7.96 (1H, br s), 9.98 (1H, br s)

MS (ESI-) m/z : 374 (M-H)

Example 70

N-Hydroxy-2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxamide (203 mg)

mp : 124-126°C

NMR ($CDCl_3$, δ) : 1.22-1.38 (1H, m), 1.45-1.66 (2H, m), 1.70-1.83 (1H, m), 1.88-1.98 (1H, m), 2.43-2.55 (1H, m), 2.60-2.75 (2H, m), 2.80 (1H, d, J=14Hz), 3.15 (1H, d, J=14Hz), 6.90 (2H, d, J=8Hz), 7.00 (2H, d, J=8Hz), 7.05-7.15 (3H, m), 7.33 (2H, t, J=8Hz), 9.47 (1H, s)

MS (ESI-) m/z : 342 (M-H)

Example 71

N-Hydroxy-2-(4-biphenylylmethyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxamide 1,1-dioxide (78 mg)

mp : 101-104°C

NMR (DMSO-d_6, δ) : 1.58-2.18 (6H, m), 3.06-3.17 (1H, m), 3.39 (1H, d, J=14Hz), 3.49-3.64 (1H, m), 3.65 (1H, d, J=14Hz), 7.31 (2H, d, J=8Hz), 7.37 (1H, d, J=8Hz), 7.46 (2H, t, J=8Hz), 7.59 (2H, d, J=8Hz), 7.65 (2H, d, J=8Hz), 9.20 (1H, s)

MS (ESI-) m/z : 358 (M-H)

Example 72

N-Hydroxy-2-(4-phenoxyphenyl)-1,3-dithian-2-acetamide (88 mg)

NMR (DMSO-d_6, δ) : 2.27-2.38 (2H, m), 3.43 (2H, s), 3.60-3.67 (2H, m), 3.80-3.88 (2H, m), 7.00 (2H, d, J=8.0Hz), 7.10 (2H, d, J=8.0Hz), 7.22 (1H, dd, J=8.0, 8.0Hz), 7.45 (2H, dd, J=8.0, 8.0Hz), 8.04 (2H, d, J=8.0Hz), 8.94 (1H, s)

MS (ESI) m/z : 360.1 (M-H)

Example 73

N-Hydroxy-2-[5-(4-chlorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (200 mg)

NMR (DMSO-d_6, δ) : 1.74-2.02 (4H, m), 2.96-3.52 (6H, m), 7.22 (1H, d, J=3.6Hz), 7.47-7.53 (3H, m), 7.67 (2H, d, J=8.7Hz), 8.85 (1H, s), 10.59 (1H, s)

MS (ESI-) m/z : 398 (M-H)

Example 74

N-Hydroxy-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (140 mg)

NMR (DMSO-d_6, δ) : 1.73-2.00 (4H, m), 2.26-2.33 (1H, m), 2.86-2.96 (2H, m), 3.11-3.23 (2H, m), 3.40-3.45 (1H, m), 7.03 (1H, d, J=3.9Hz), 7.22 (1H, d, J=3.9Hz), 8.86 (1H, s), 10.57 (1H, s)

MS (ESI-) m/z : 366 (M-H)

Example 75

(2R or 2S)-N-Hydroxy-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (65 mg) from (2R or 2S)-N-(2-tetrahydropyranyloxy)-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (80 mg) obtained in Example 53

$[\alpha]_D^{25}$: -17.1° (C=0.485, DMF)

NMR (DMSO-d_6, δ) : 1.73-2.00 (4H, m), 2.26-2.33 (1H, m), 2.86-2.96 (2H, m), 3.11-3.23 (2H, m), 3.40-3.45 (1H, m), 7.03 (1H, d, J=3.9Hz), 7.22 (1H, d, J=3.9Hz), 8.86 (1H, s), 10.57 (1H, s)

MS (ESI-) m/z : 366 (M-H)

Optical purity : 95% ee

Analytical chiral HPLC :

column : Chiralpak AS (4.6 x 250 mm, Daicel Chemical Industries, Ltd.)

eluent : n-hexane-ethanol-TFA (700:300:1)
flow rate : 1.0 ml/minute
detection : 220 nm

The following compounds were obtained in a similar manner to that of Preparation 1-4).

Example 76

2-[4-(4-Fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (450 mg)

NMR ($CDCl_3$, δ) : 1.87-2.21 (4H, m), 2.67-2.85 (2H, m), 3.03-3.15 (2H, m), 3.21 (1H, d, J=16Hz), 3.62 (1H, d, J=16Hz), 6.94-7.04 (6H, m), 7.59 (2H, d, J=9Hz)

MS (ESI-) m/z : 377 (M-H)

Example 77

2-[4-(4-Bromophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide

NMR ($CDCl_3$, δ) : 1.75-2.02 (4H, m), 2.08-2.21 (2H, m), 2.63-2.85 (2H, m), 3.02-3.16 (2H, m), 3.21 (1H, d, J=16Hz), 3.60 (1H, d, J=16Hz), 6.92 (2H, d, J=9Hz), 7.00 (2H, d, J=9Hz), 7.46 (2H, d, J=9Hz), 7.60 (2H, d, J=9Hz)

MS (ESI-) m/z : 439

Example 78

2-(4-Methoxyphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid

NMR ($CDCl_3$, δ) : 1.71-2.00 (4H, m), 2.07-2.20 (2H, m), 2.60-2.86 (2H, m), 2.99-3.14 (2H, m), 3.19 (1H, d, J=15.5Hz), 3.60 (1H, d, J=15.5Hz), 3.81 (3H, s), 6.82 (2H, d, J=9Hz), 7.56 (2H, d, J=9Hz)

MS (ESI-) m/z : 297

Example 79

2-[5-(4-Fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid

NMR ($CDCl_3$, δ) : 1.70-2.02 (2H, m), 2.09-2.24 (2H, m), 2.67-2.86 (2H, m), 3.02-3.20 (2H, m), 3.19 (1H, d, J=15Hz), 3.46 (1H, d, J=15Hz), 7.06 (2H, dd, J=8Hz, 8Hz), 7.15 (1H, d, J=3Hz), 7.21 (1H, d, J=3Hz), 7.46-7.62 (2H, m)

MS (ES-) m/z : 367 (M-H)

Example 80

2-(4-Biphenylyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (0.33 g)

NMR ($CDCl_3$, δ) : 1.80-2.01 (2H, m), 2.11-2.19 (2H, m), 2.69-2.76 (1H, m), 2.82-2.92 (1H, m), 3.02-3.16 (2H, m), 3.24 (1H, d, J=15.6Hz), 3.67 (1H, d, J=15.6Hz), 7.37-7.46 (2H, m), 7.58-7.63 (4H, m), 7.71 (2H, d, J=9Hz)

MS (ESI-) m/z : 343 (M-H)

Example 81

2-[4-(4-Chlorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (275 mg)

NMR ($CDCl_3$, δ) : 1.79-2.00 (2H, m), 2.10-2.18 (2H, m), 2.66-2.89 (2H, m), 3.02-3.14 (2H, m), 3.23 (1H, d, J=16Hz), 3.65 (1H, d, J=16Hz), 7.40 (2H, d, J=9Hz), 7.50 (2H, d, J=8.5Hz), 7.57 (2H, d, J=8.5Hz), 7.70 (2H, d, J=9Hz)

MS (ESI-) m/z : 377 (M-H)

Example 82

2-[4-(4-Bromophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (105 mg)

NMR ($CDCl_3$, δ) : 1.70-2.20 (4H, m), 2.72-2.92 (2H, m), 3.05-3.16 (2H, m), 3.25 (1H, d, J=16Hz), 3.67 (1H, d, J=16Hz), 7.44 (2H, d, J=9Hz), 7.55-7.58 (4H, m),

7.71 (2H, d, J=9Hz)

MS (ESI-) m/z : 421 (M-H)

Example 83

2-[4-(4-Fluorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (220 mg)

NMR ($CDCl_3$, δ) : 1.80-2.18 (4H, m), 2.69-2.91 (1H, m), 3.04-3.16 (3H, m), 3.24 (1H, d, J=16Hz), 3.66 (1H, d, J=16Hz), 7.12 (2H, dd, J=9, 9Hz), 7.52-7.58 (4H, m), 7.70 (2H, d, J=8.5Hz)

MS (ESI-) m/z : 361 (M-H)

Example 84

A mixture of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (56 g), potassium permanganate (48.8 g) and benzyltrimethylammonium chloride (2.87 g) in water-methylene chloride (2:1, 1.5 ℓ) was stirred for 3 hours at room temperature. After the reaction mixture was poured into saturated sodium sulfite solution (500 ml), the solution was acidified with 4N hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with chloroform (400 ml x 2). The combined organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The resulting residue was purified with silica gel column chromatography (eluent : chloroform-methanol 10:1) to give 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (17.2 g) as colorless crystal.

mp : 191-193°C

Example 85

N-Hydroxy-2-(4-phenoxyphenyl)-1,3-dithiane-2-acetamide 1,1,3,3-tetraoxide (56 mg) was obtained in a similar manner to that of Preparation 1-4).

NMR (DMSO-d_6, δ) : 2.27-2.38 (2H, m), 3.43 (2H, s),

3.60-3.67 (2H, m), 3.80-3.88 (2H, m), 7.00 (2H, d, J=8.0Hz), 7.10 (2H, d, J=8.0Hz), 7.22 (1H, dd, J=8.0, 8.0Hz), 7.45 (2H, dd, J=8.0, 8.0Hz), 8.04 (2H, d, J=8.0Hz), 8.94 (1H, s)

MS (ESI) m/z : 424.1 (M-H)

Example 86

To a solution of 2-[4-(4-fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (300 mg) in MeOH was added dropwise titanium (III) chloride (2.67 ml) (10 wt. % solution in hydrochloric acid) in MeOH and hydrogen peroxide (0.69 ml)(30% aqueous solution) at room temperature. After being stirred for 15 minutes, the reaction is stopped by adding water. The reaction mixture is extracted with EtOAc and the solution was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent : 5% MeOH in $CHCl_3$) to give 2-[4-(4-fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1-oxide (150 mg) as an amorphous.

NMR ($CDCl_3$, δ) : 1.55-1.76 (4H, m), 2.45-2.62 (4H, m), 3.05-3.07 (2H, m), 6.95-7.07 (6H, m), 7.39 (2H, d, J=9Hz)

MS (ESI-) m/z : 361 (M-H)

Example 87

2-[5-(4-Chlorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (1.95 g) was obtained in a similar manner to that of Preparation 1-4).

NMR (DMSO-d_6, δ) : 1.76-1.90 (4H, m), 3.16-3.55 (6H, m), 7.19 (1H, d, J=3.6Hz), 7.47-7.52 (3H, m), 7.68 (2H, d, J=8.4Hz)

Example 88

2-(5-Bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (6.0 g) was obtained in a similar

manner to that of Preparation 1-4).

NMR (DMSO-d_6, δ) : 1.74-1.87 (4H, m), 2.30-2.37 (1H, m), 3.07-3.56 (5H, m), 7.02 (1H, d, J=4.2Hz), 7.21 (1H, d, J=4.2Hz)

MS (ESI-) m/z : 351 (M-H)

Example 89

A mixture of 2-[4-(4-bromophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (130 mg), 4-fluorobenzeneboronic acid (49.7 mg) and tetrakis(triphenylphosphine)palladium(0) (3.4 mg) in a mixture of 1,2-dimethoxyethane (0.5 ml) and 2M aqueous sodium carbonate (0.5 ml) was refluxed for 6 hours. The mixture was acidified with 4N hydrochloric acid to pH 3 and extracted with ethyl acetate. The separated organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo to give 2-[4-[4-(4-fluorophenyl)phenoxy]phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (116 mg) as an oil.

NMR ($CDCl_3$, δ) : 1.75-2.02 (4H, m), 2.08-2.21 (2H, m), 2.64-2.84 (2H, m), 3.01-3.17 (2H, m), 3.23 (1H, d, J=15Hz), 3.62 (1H, d, J=15Hz), 7.04 (2H, d, J=9Hz), 7.07-7.16 (4H, m), 7.41-7.56 (4H, m), 7.61 (2H, d, J=9Hz)

MS (ESI-) m/z : 453

Example 90

1.6M n-Butyl lithium in hexane (1.63 ml) was added dropwise to a solution of diisopropylamine (261 mg) in THF (10 ml) under ice-bath cooling and a nitrogen atmosphere. After being stirred under the same condition for 30 minutes, a solution of methyl 3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide (450 mg) in THF (8 ml) was added therein and the mixture was stirred for 45 minutes under dry ice-acetone cooling. A solution of 4-phenoxybenzyl bromide

(719 mg) in THF (8 ml) was added to this mixture under the same condition. After the mixture was stirred for 2 hours under the same temperature for 2 hours under ice-bath cooling and for 2 hours at room temperature, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The resulting mixture was extracted with AcOEt. The extract was washed with 5% hydrochloric acid, 1M sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel (SiO_2) column chromatography (eluent : hexane-AcOEt, 6:1) to give methyl 2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide (745 mg) as an oil.

NMR ($CDCl_3$, δ) : 1.68-1.92 (2H, m), 2.02-2.34 (4H, m), 3.10-3.30 (2H, m), 3.17 (1H, d, J=14Hz), 3.74 (1H, d, J=14Hz), 3.83 (3H, s), 6.91 (2H, d, J=8Hz), 7.00 (2H, d, J=8Hz), 7.06-7.18 (3H, m), 7.34 (2H, t, J=8Hz)

Example 91

Methyl 2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylate (605 mg) was obtained in a similar manner to that of Example 90.

NMR ($CDCl_3$, δ) : 1.46-1.82 (4H, m), 1.86-1.96 (1H, m), 2.28-2.40 (1H, m), 2.52-2.62 (1H, m), 2.69-2.80 (1H, m), 3.07 (2H, s), 3.71 (3H, s), 6.89 (2H, d, J=8Hz), 7.00 (2H, d, J=8Hz), 7.06-7.14 (3H, m), 7.33 (2H, t, J=8Hz)

Example 92

Methyl 2-(4-biphenylylmethyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide (250 mg) was obtained in a similar manner to that of Preparation 90.

NMR ($CDCl_3$, δ) : 1.72-1.93 (2H, m), 2.06-2.20 (3H, m), 2.25-2.37 (1H, m), 3.12-3.30 (2H, m), 3.24 (1H, d,

J=14Hz), 3.81 (1H, d, J=14Hz), 3.86 (3H, s), 7.23 (2H, d, J=8Hz), 7.30-7.38 (1H, m), 7.43 (2H, t, J=8Hz), 7.49-7.58 (4H, m)

Example 93

To a stirred solution of ethyl 3-hydroxy-3-(4-methoxyphenyl)-7-mercaptoheptanoate (3.00 g) in dichloromethane (20 ml) was added trifluoroacetic acid (1 ml) at room temperature under nitrogen. After 1 hour, the mixture was quenched by the addition of triethylamine (1 ml) with ice cooling and concentrated in vacuo. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The separated organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo. The obtained oil was purified by column chromatography on silica gel (eluted with 5 to 10% ethyl acetate in n-hexane) to give ethyl 2-(4-methoxyphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetate (2.216 g) as an oil.

NMR ($CDCl_3$, δ) : 1.05 (3H, t, J=7Hz), 1.50-1.84 (5H, m), 2.25-2.36 (1H, m), 2.45-2.71 (2H, m), 2.79 (1H, d, J=14Hz), 2.91 (1H, d, J=14Hz), 3.81 (3H, s), 3.93 (2H, q, J=7Hz), 6.88 (2H, d, J=9Hz), 7.55 (2H, d, J=9Hz)

Example 94

To a mixture of ethyl 3-oxo-3-(4-phenoxyphenyl)-propanoate (500 mg) and 1,3-propanedithiol (2 ml) was added boron trifluoride diethyl etherate (2 ml) at 0°C. After being stirred at ambient temperature for 3 hours, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by column chromatography on silica gel 60 (50 g) (eluent :

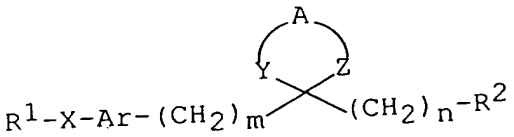
ethyl acetate:hexane (1:10)) to give ethyl 2-(4-phenoxyphenyl)-1,3-dithian-2-acetate (370 mg) as a yellow oil.

NMR ($CDCl_3$, δ) : 1.12 (3H, t, J=7.0Hz), 1.94-2.01 (2H, m), 2.75-2.81 (4H, m), 3.13 (2H, s), 4.00 (2H, q, J=7.0Hz), 6.98 (2H, d, J=8.5Hz), 7.03 (2H, d, J=7.0Hz), 7.12 (1H, dd, J=7.0, 7.0Hz), 7.34 (2H, dd, J=7.0, 7.0Hz), 7.88 (2H, d, J=8.5Hz)

MS (ESI) m/z : 374 (M-H)

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula :



(I)

in which R^1 is lower alkyl, halogen, optionally substituted heterocyclic group or optionally substituted aryl,

R^2 is carboxy, protected carboxy or amidated carboxy,

Ar is optionally substituted aryl or optionally substituted heterocyclic group,

A is lower alkylene,

X is oxa or a single bond,

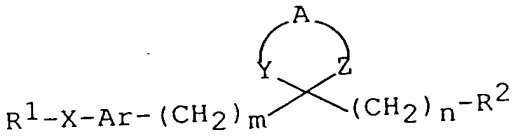
Y is thia, sulfinyl or sulfonyl,

Z is lower alkylene, thia, sulfinyl or sulfonyl,

m and n are each an integer of 0 to 6, and $1 \leqq m+n \leqq 6$,

and its salt.

2. A process for the preparation of a compound of the formula :

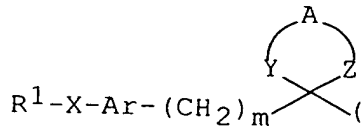


(I)

in which R^1, R^2, Ar, A, X, Y, Z, m and n are each as defined in Claim 1,

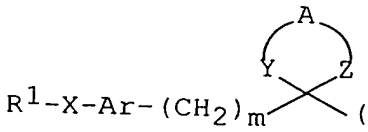
which comprises

(1) subjecting a compound of the formula :



(I-a)

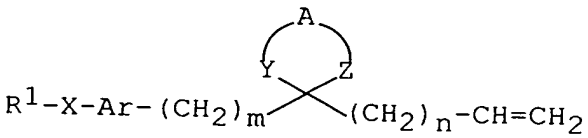
or a salt thereof to removal reaction of the carboxy-protective group, to give a compound of the formula :



(I-b)

or a salt thereof; or

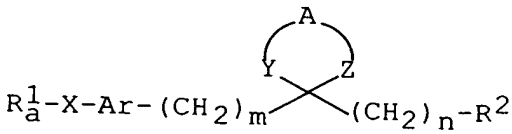
(2) oxidating the vinyl group of a compound of the formula :



(II)

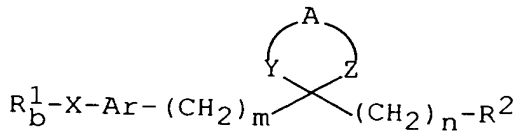
or a salt thereof, to give a compound of the above formula (I-b) or a salt thereof; or

(3) reducing a compound of the formula :



(I-c)

or a salt thereof, to give a compound of the formula :



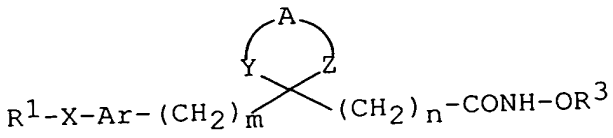
(I-d)

or a salt thereof; or

(4) reacting a compound of the above formula (I-b) or its reactive derivative at the carboxy-group, or a salt thereof, with a compound of the formula :

$$NH_2\text{-}OR^3 \qquad (IV)$$

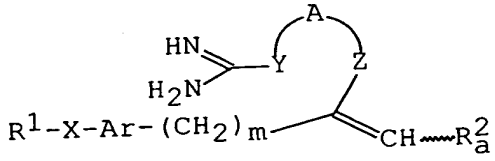
or its reactive derivative at the amino-group, or a salt thereof, to give a compound of the formula :



(I-e)

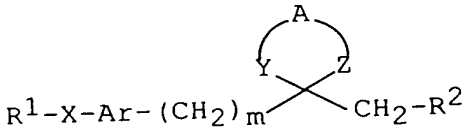
or a salt thereof; or

(5) cyclizing a compound of the formula :



(III)

or a salt thereof, to give a compound of the formula :

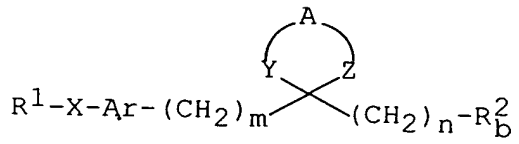


(I-f)

or a salt thereof; or

(6) reacting a compound of the above formula (I-b) or its

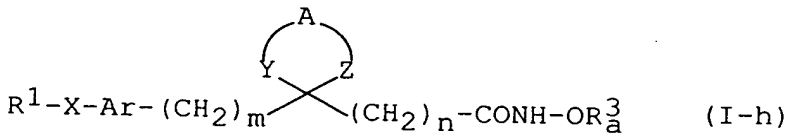
reactive derivative at the carboxy-group, or a salt thereof, with an optically active amine or its reactive derivative at the amino-group, or a salt thereof, to give a compound of the formula :



(I-g)

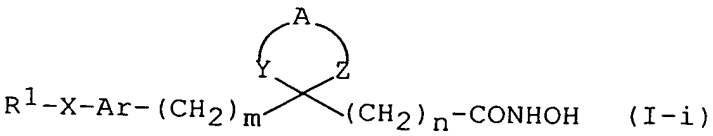
or a salt thereof; or

(7) subjecting a compound of the formula :



(I-h)

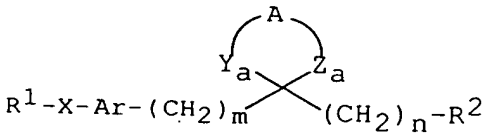
or a salt thereof to removal reaction of the hydroxy-protective group, to give a compound of the formula :



(I-i)

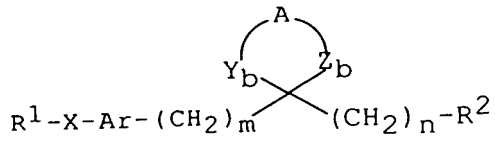
or a salt thereof; or

(8) oxidating a compound of the formula :



(I-j)

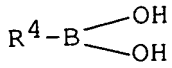
or a salt thereof, to give a compound of the formula :



(I-k)

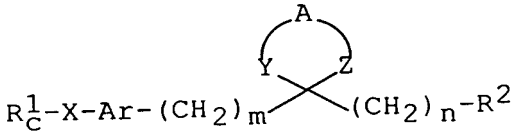
or a salt thereof; or

(9) reacting a compound of the above formula (I-c) or a salt thereof, with a compound of the formula :



(V)

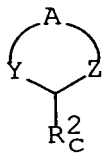
to give a compound of the formula :



(I-l)

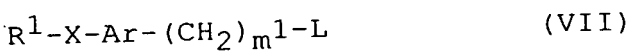
or a salt thereof; or

(10) reacting a compound of the formula :



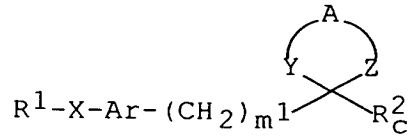
(VI)

or a salt thereof, with a compound of the formula :



(VII)

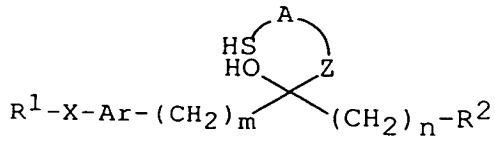
or a salt thereof, to give a compound of the formula :



(I-m)

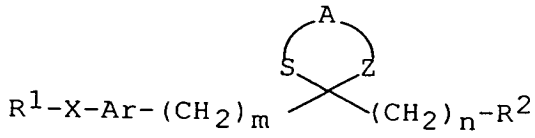
or a salt thereof; or

(11) cyclizing a compound of the formula :



(VIII)

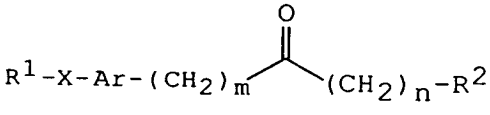
or a salt thereof, to give a compound of the formula :



(I-n)

or a salt thereof; or

(12) reacting a compound of the formula :

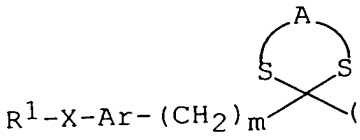


(IX)

or a salt thereof, with a compound of the formula :

HS-A-SH (X)

to give a compound of the formula :



(I-o)

or a salt thereof;

in which R^1, R^2, Ar, A, X, Y, Z, m and n are each as defined above,

R^1_a is haloaryl,

R^1_b is aryl,

R^1_c is aryl substituted by optionally substituted aryl,

R^2_a is protected carboxy,

R^2_b is optically active amide,

R^2_c is protected carboxy,

R^3 is hydrogen or hydroxy-protective group,

R^3_a is hydroxy-protective group,

R^4 is optionally substituted aryl,

Y_a is thia, sulfinyl or sulfonyl,

Z_a is methylene, thia, sulfinyl or sulfonyl, provided that at least one of Y_a and Z_a is thia or sulfinyl,

Y_b is thia, sulfinyl or sulfonyl,

Z_b is methylene, thia, sulfinyl or sulfonyl, provided that at least one of Y_b and Z_b is sulfinyl or sulfonyl,

L is a leaving group, and

m^1 is an integer of 1 to 6.

3. A pharmaceutical composition which comprises the compound of Claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

4. A process for preparing a pharmaceutical composition

which comprises admixing the compound of Claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier or excipient.

5. Use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof as a medicament.

6. Use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof as an inhibitor of matrix metalloproteinases (MMP) or tumor necrosis factor α (TNF α).

7. Use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof for manufacturing a medicament for treating and/or preventing MMP- or TNF α-mediated diseases.

8. A method for treating and/or preventing MMP- or TNF α-mediated diseases which comprises administering the compound of Claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

Dated this 7th day of January 1999

Fujisawa Pharmaceutical Co., Ltd.

By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant